STUDIES IN THE PSYCHOBIOLOGY OF THE NIGROSTRIATAL DOPAMINE SYSTEM IN THE RAT

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STATEMENT IN TERMS OF Ph.D. REGULATION 2.5.15 OF THE POSTGRADUATE STUDY PROGRAMME OF THE UNIVERSITY OF EDINBURGH.

The work presented in this thesis has been composed by myself with the following exceptions:-

A. The estimations of dopamine and norepinephrine concentrations in respect of four of the rats used in Experiment I of Chapter 4 (see 4:2(A)(iv) and 4:3(A)(ii)) were performed by Mrs. A. Wright.

B. The estimations of dopamine and norepinephrine concentrations and of choline acetyltransferase and glutamic acid decarboxylase activities, described in Chapter 7 (see 7:2(A)(v); 7:3(A)(i); 7:2(B)(v), and 7:3(B)(iii)) were performed by Mrs. A. Wright.

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ABSTRACT

This thesis presents experiments designed to ascertain, in the rat, the role of the nigrostriatal DA system in ingestive behaviour and body weight regulation, operant learning, sensorimotor control of behaviour and spatial behaviour.

In some experiments a 6-OHDA lesion of the medial forebrain bundle was used to destroy the nigrostriatal DA system on one side; in some other experiments the nigrostriatal system was disrupted postsynaptically on one side by injecting kainic acid unilaterally into the striatum. The effects of these lesions were: (a) the 6-OHDA lesion increased food spillage and decreased food intake and body weight; (b) the kainate lesion after some days caused an increase in food intake and body weight; (c) kainate-lesioned, but not 6-OHDA-lesioned, ss consistently preferred to operate the contralateral lever in a two-lever Skinner box; (d) both lesions produced a reversal of forepaw preferences when given in the hemisphere opposite to the normally preferred forepaw; (e) after either lesion, rats rotated mainly ipsiversively, but this effect was stronger in 6-OHDA-lesioned ss; (f) rats trained 2wks or 12wks after 6-OHDA lesion took, on the average, longer time than controls to acquire a food-rewarded lever-pressing response; those with a 12-wk-old lesion showed a preference for the ipsilateral forepaw, but those with a 2-wk-old lesion as a group displayed random forepaw use; (g) rats lesioned with 6-OHDA on the side opposite to the normally preferred arm of a T-maze exhibited a reversal of side preferences.

In other experiments, intact rats treated chronically with the DA receptor blocker, haloperidol, exhibited reductions of food spillage and/

and food and water intake, and an apparent facilitation of body weight.

It is suggested that the nigrostriatal DA system is involved in ingestive behaviour and body weight regulation, learning, sensorimotor control and spatial behaviour. The nature of nigrostriatal dopaminergic involvement is discussed.

GENERAL INTRODUCTION

1:1. THE RISE OF DOPAMINE

Following the identification of norepinephrine (NE) as a normal constituent of the mammalian brain (Holtz, 1950) and the demonstration that it has a unique regional distribution in the brain (Vogt, 1954) this catecholamine was widely investigated in terms of its possible specialised CNS functions. Over the years central NE was implicated in a variety of behavioural functions, such as feeding (Antelman, Szechtman, Chin and Fisher, 1975), reward processes (Arbuthnott, Crow and Spear, 1970; Ritter and Stein, 1973), aggression (Geyer and Segal, 1974; Masur, Czeresnia, Skitnevsky and Carlini, 1974) and active avoidance (Smith, Cooper and Breese, 1973).

Although biochemical studies by Montagu (1957) had indicated the existence of dopamine (DA) in brain tissue, DA owes its rise largely to the work of Carlsson, Lindqvist, Magnusson and Waldeck (1958), who found out that the sedative action of reserpine, a monoamine depletor (Pletscher, Shore and Brodie, 1955; Holzbauer and Vogt, 1956) was not due to NE depletion. When Carlsson and co-workers administered the catecholamine precursor, DOPA, to reserpinised rabbits, they found that this treatment reversed the sedative effect of reserpine but did not at the same time replenish NE stores. Their finding caused attention to be directed to DA, which is an intermediate product in the synthesis of NE. These investigators further developed a fluorimetric method for DA measurement, and using this method showed that DA occurs in the brain in appreciable amounts (Carlsson and Waldeck, 1958; Carlsson et al., 1958). Following further work Carlsson showed that brain DA has

a/

a regional distribution that is markedly different from that of NE, with 80% of the total brain content of DA occurring in the basal ganglia (Carlsson, 1959). This significant finding was confirmed by the first detailed biochemical mapping of DA and NE systems of the brain (Bertler and Rosengren, 1959). It seemed evident, therefore, that the newly discovered catecholamine has significant CNS functions and deserved to be investigated in its own right.

Since then brain DA has been implicated in a wide spectrum of behavioural functions. For example, this catecholamine, which constitutes about 50% of the catecholamine content of the CNS of most mammals, has been shown to be involved in ingestive behaviour (Ungerstedt, 1971a), reward mechanisms (Phillips and Fibiger, 1973; Stein, Belluzzi, Ritter and Wise, 1974; Yokel and Wise, 1975), arousal (Jouvet, 1972; Stricker and Zigmond, 1976), sensorimotor functions (Marshall, Richardson and Teitelbaum, 1974) and spatial behaviour (Arbuthnott and Ungerstedt, 1969; Zimmerberg, Glick and Jerussi, 1974).

1:2. BRAIN DOPAMINE AND PSYCHOMOTOR BEHAVIOUR

Reports from several laboratories have shown that brain DA is involved in psychomotor behaviour. It is known that drugs which increase activity at central DA synapses enhance, whereas drugs which depress activity at these synapses depress, both electrocortical arousal and behavioural responsiveness (Jouvet, 1972). Also apomorphine, which is a direct stimulant of DA receptors (Anden, Fuxe, Hokfelt and Rubensson 1967; Ernst, 1967) and amphetamine, which causes the release of catecholamines (Carlsson, 1970; Glowinski, 1970) produce hyperactivity and stereotyped behaviour (Ernst and Smelik, 1966; Fog and Pakkenberg, 1971;/

1971; Fog, Randrup and Pakkenberg, 1967, Fuxe and Ungerstedt, 1970; Randrup and Munkvad, 1968; Randrup and Munkvad, 1970; Ungerstedt, Butcher, Butcher, Anden and Fuxe, 1969). The hyperactivity and stereotyped behaviour caused by these sympathomimetic drugs can be suppressed by the administration of neuroleptic agents, which are believed to inhibit the postsynaptic DA receptors (Anden, Butcher, Corrodi, Fuxe, and Ungerstedt, 1970; Carlsson and Linqvist, 1963; Corrodi, Fuxe and Hokfelt, 1967).

Also it has been reported (Fuxe and Ungerstedt, 1970) that bilateral microinjection of low doses of DA or amphetamine into the striata of intact rats pretreated with the monoamine oxidase inhibitor nialamide produced forward locomotion. Prior administration of haloperidol or chlorpromazine prevented the effects of intrastriatally applied DA or amphetamine. Injection of DA into extrastriatal structures such as the thalamus or neocortex did not produce the effects obtained through instrastriatal treatment.

Furthermore, both alpha-methyltyrosine, an hydroxylase inhibitor (Spector, Sjoerdsma and Udenfriend, 1965), and reserpine make animals akinetic. L-dopa reverses the akinetic affect of alpha-methyltyrosine (Bedard, Larochelle, Poirier and Sourkes, 1970; Larochelle, Bedard, Poirier and Sourkes, 1971) and of reserpine (Carlsson et al., 1958). This anti-akinetic action of L-dopa does not appear to be mediated through NE, as Carlsson and his co-workers did not observe any replenishment of NE in their reserpinized rabbits after the administration of L-dopa.

As well as purely pharmacological studies several experiments involving the destruction of the nigrostriatal DA system strongly

suggest that central dopaminergic mechanisms play an important role in psychomotor functioning. Thus, for example, animals bilaterally depleted of telencephalic DA through the central administration of 6-OHDA display an increase in the amount of motor activity elicited by a given dose of apomorphine (Shoenfeld and Uretsky, 1972; Stricker and Zigmond, 1976), and this has been shown to be due to the development of supersensitivity of DA agonists by the postsynaptic DA receptors following nigrostriatal damage (Ungerstedt, 1971c).

1:3. NIGROSTRIATAL ASYMMETRY AND SPACE-RELATED BEHAVIOUR

Asymmetry between the nigrostriatal DA systems of the two hemispheres has been shown in several laboratories to make animals rotate away from the "dominant" side. Thus, for example, animals with a unilateral lesion of the nigrostriatal DA system tend to circle toward the lesion side and this tendency is accentuated by amphetamine owing to a widening of the difference in DA release and consequent postsynaptic DA receptor stimulation between the two sides (Ungerstedt, 1971e). Because the postsynaptic DA receptors on the lesion side acquire a supersensitivity to DA agonists (Ungerstedt, 1971c) peripheral treatment with a direct-acting sympathomimetic agent such as apomorphine produces contraversive circling in such animals through causing greater postsynaptic DA receptor activity on the lesion side. Also, in intact rats, unilateral electrical stimulation of the nigrostriatal DA pathway (Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1969) or unilateral chemical stimulation of the striatum through direct intrastriatal application of DA or amphetamine after pretreatment with the monoamine oxidase inibitor nialamide (Fuxe and Ungerstedt, 1970) leads to contraversive rotation.

In addition to directional preference in circling, side preference in a T-maze or in a two-lever operant behaviour box has been shown to be determined by asymmetry between the two nigrostriatal DA systems in an animal. Thus electrical stimulation of the nigrostriatal DA system on one side elicits contraversive side preference (Zimmerberg and Glick 1975), whereas a unilateral lesion of the nigrostriatal DA system produces ipsilateral side preference (Hansing, Schwartzbaum and Thompson, 1968; Zimmerberg, Glick and Jerussi, 1974).

Throughout the present thesis the term "space-related behaviour" refers to rotational behaviour, lever choice in a two-lever Skinner box and side- and goal-preferences in a T-maze.

1:4. NIGROSTRIATAL DAMAGE AND THE LATERAL HYPOTHALAMIC SYNDROME

The lateral hypothalamic (LH) syndrome refers essentially to a set of both short and long-term ingestive deficits which result from lesions localized to the LH (Anand and Brobeck, 1951; Epstein, 1971; Teitelbaum and Epstein, 1962). LH animals will not eat (aphagia) and will not drink (adipsia). Recovery from the initial aphagia and adipsia, when it does take place, is a gradual process occurring in progressive stages. Even after the LH animals resume voluntary eating and drinking there remain a number of persistent residual deficits, such as a subnormal body weight and an impairment of the ability to respond to dehydrational and glucoprivic challenges.

Ungerstedt (1971a) has shown that extensive bilateral damage to the nigro-neostriatal pathway produces aphagia and adipsia, and many of the long-term deficits attributed to LH damage. Ungerstedt (1971a) lesioned his subjects through intranigral or medial forebrain bundle (MFB) injections/

injections of 6-hydroxydopamine (6-OHDA), a neurotoxin that selectively destroys catecholamine-containing neurons (Ungerstedt, 1968, 1971b). On the basis of his results Ungerstedt proposed that the aphagia and adipsia resulting from LH lesions were caused by damage to the ascending catecholamine pathways passing through the LH, notably the nigrostriatal DA pathway. Ungerstedt's findings have since been confirmed by results published from many other laboratories (Fibiger, Zis and McGeer, 1973; Marshall, Richardson and Teitelbaum, 1974; Oltmans and Harvey, 1972, Stricker, 1976; Stricker and Zigmond, 1974; 1976; Zigmond and Stricker, 1972).

Obviously, the intake of food and water as a survival orientated function involves two inalienable elements. These are motivational arousal and sensorimotor control. The cessation of feeding and drinking observed following nigrostriatal or other lesions may in the final analysis reflect a disruption of either or both of these elements. Although the precise nature of lesion-induced disruption of ingestive behaviour has not yet been catalogued, there are published experimental findings which appear to suggest the over-riding importance of the motivational or else the sensorimotor element.

Taking motivation first, some of the studies of Stricker and Zigmond are of great interest. More than 90% depletion of striatal DA is required to produce aphagia and adipsia through intraventricular administration of 6-OHDA (Zigmond and Stricker, 1973). Stricker and Zigmond (1976) have suggested that the inability to initiate ingestive behaviour which is displayed by animals deprived of brain catecholamines through central administration of 6-OHDA is due to drastically reduced availability/

availability of these substances for the stimulation of postsynaptic receptors. These authors went on to propose that the deficit in ingestive behaviour observed in 6-OHDA-lesioned animals is due to the disruption of the arousal component of behaviour. If their proposal is correct it may just be that the aphagia and adipsia encountered following bilateral nigrostriatal damage have a motivational element. In other words, since central arousal is an essential feature of motivated behaviour and since motivation is normally necessary for ingestive behaviour to occur it should not then be surprising that animals sustaining a depletion of brain catecholamines are aphagic and adipsic. Thus a neurochemical interpretation of the disruption of ingestive behaviour by 6-OHDA-induced nigrostriatal damage might apply directly and specifically to an impairment of motivation following such lesions.

The so-called neurochemical interpretation appears to be supported also by findings from a series of purely psychopharmacological experiments.

Alpha-adrenergic receptor stimulants such as NE (Booth, 1968; Grossman, 1960; Leibowitz, 1973; 1975a), and epinephrine (Grossman, 1964; Leibowitz, 1975b) can induce eating in sated animals when applied to the medial portion of the hypothalamus. A potentiation of feeding is obtained by the medial hypothalamic application of the endogenous catecholamine releasers, ~~tranylcypromine (Leibowitz, 1971) and~~ e.g. d-amphetamine (Leibowitz, 1970a). On the other hand, LH administration of catecholamine agonists such as DA (Kruk, 1973; Hansen and Whishaw, 1973), isoproterenol (Leibowitz, 1970a; 1972; Margules, 1970; Goldman, Lehr and Friedman, 1971; Jackson and Robinson, 1971), or

NE/

NE (Margules, 1970; Leibowitz, 1971), or of the indirect catecholamine stimulant amphetamine (Leibowitz, 1970a; 1970b; Booth, 1968) suppresses feeding behaviour in hungry animals. The interesting thing about these psychopharmacological studies is that local applications of exogenous catecholamingergic substances to restricted areas of the brain have been found to affect feeding and drinking behaviour. In view of this fact, it might be expected that the depletion of endogenous catecholamines would disrupt ingestive behaviour as a result of the mere absence of these substances at the sites where they normally occur in the brain. This is a possibility worth investigating with particular reference to motivational implications.

The significance of the sensorimotor element in the explanation of the feeding and drinking deficits associated with nigrostriatal damage is also suggested by the results of a number of recent studies. Certain CNS structures have been shown to be involved both in ingestive behaviour and in purely sensorimotor functions. Notable in this regard is the pallidum. A unilateral lesion of the pallidum produces a complete loss of the capacity to use the forelimb contralateral to the lesion (Levine and Schwartzbaum, 1973; Levine, Ferguson, Kreinick, Gustafson and Schwartzbaum, 1971), and bilateral pallidal lesions cause aphagia (Levine and Schwartzbaum, 1973; Levine et al., 1971). Levine and Schwartzbaum found moreover that animals with pallidal damage display an impairment of the capacity to use the musculature of the mouth region. Obviously, an animal that loses the sensorimotor control of those organs of the body essential to ingestive behaviour cannot eat or drink. Thus sensorimotor impairment could account for part or all of the aphagia and adipsia associated with pallidal damage. A similar explanation might conceivably/

conceivably apply to the cessation of feeding and drinking observed following bilateral nigrostriatal pathway damage. This again poses a question worth answering.

1:5. THE EXTRAPYRAMIDAL NETWORK AND THE NIGROSTRIATAL DOPAMINE SYSTEM IN MOTOR CONTROL.

The extrapyramidal system is composed mainly of the caudate putamen and pallidum interconnected with the thalamic intralaminar nuclei, the subthalamic nucleus and the substantia nigra. Fibres from the internal segment of the pallidum reach the thalamic intralaminar nuclei (Nauta and Mehler, 1966) while the external pallidum sends fibres to the subthalamic nucleus (Ranson and Ranson, 1939) which in turn projects mainly to both regions of the pallidum. (Vogt and Vogt, 1920; Carpenter and Strominger, 1967). The thalamic intralaminar nuclei, which also receive reticulo- and spinothalamic fibres through the ascending portion of the central tegmental track (Nauta and Kuypers, 1958; Mehler, Feferman, and Nauta, 1960), projects to the ipsilateral striatum (Powell and Cowan, 1956; Mehler, 1966). The striatum sends fibres to (Voneida, 1960; Szabo, 1962) and receives fibres from (Bedard Larochelle, Parent and Poirier, 1969) the ipsilateral substantia nigra. It should be mentioned too that the intralaminar nuclei receive inputs from the motor cortex (Astruc, 1965; Petras, 1964) and from the lateral cerebellar nuclei (Mehler, Verneir and Nauta, 1958). The pallido-fugal fibres projecting from the internal pallidum to the ventrolateral and ventral anterior regions of the thalamus and to the lateral tegmentum at the pontomesencephalic level constitutes the main outflow of the extrapyramidal system. The extrapyramidal system may be receiving corticostriatal/

corticostriatal fibres (Webster, 1961; Carman, Cowan, Powell and Webster, 1965), and the ventrolateral and ventral anterior areas of the thalamus are interconnected with the motor and premotor cortices. In the light of the above described organization and external interconnections of the extrapyramidal system (see Figure 1) there is little surprise that this sytem is involved in motor functioning. Thus, for example, bilateral destruction of the pallidum (Mettler, 1945) or of the ansa lenticularis (Carey, 1957) causes severe akinesia.

The dopaminergic neurons of the substantia nigra and nucleus parabrachialis pigmentosus send out fibres which ascend through the ventromedial tegmental area of Tsai, join the MFB within which they travel at the diencephalic level (Parent and Poirier, 1969). These fibres leave the MFB at the base of the anterior limb of the internal capsule, which structure they enter eventually. They then divide up and end in the striatum, the rostral part of the striatum receiving an input from the rostromedial area of the substantia nigra while the more lateromedial area of the substantia nigra and nucleus parabrachialis pigmentosus project to the caudal part of the striatum (Bedard et al., 1969). In the rat and other species, bilateral disruption of the nigrostriatal system causes akinesia, whether the lesion is at the level of substantia nigra (Ungerstedt, 1971a) or of the area of Tsai (Nauta, 1946; Ranson, 1939; Collins, 1954; Harrison, 1940; Ranson and Ingram, 1932) or even through intraventricular administration of 6-OHDA (Zigmond and Stricker, 1972). It should be noted, though, that as well as the nigrostriatal dopaminergic fibres some norepinephrinergic and serotoninergic fibres are known to pass through the area of Tsai and the MFB and to end in the striatum and other forebrain regions, with the/

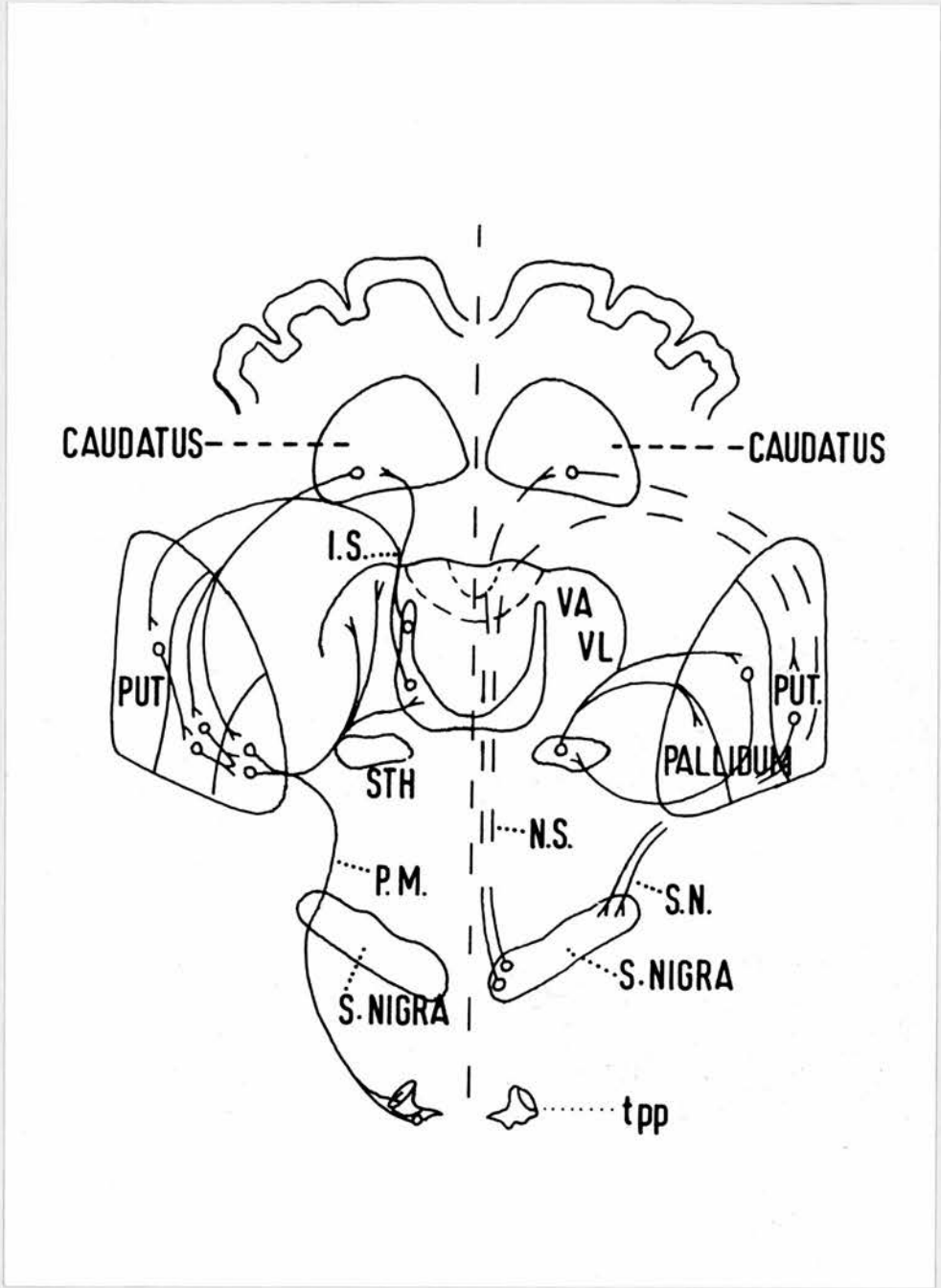


FIGURE 1:

The strio-pallidal system and its main nervous interconnections. Abbreviations: IL, intralaminar nuclei; Put, putamen; S. NIGRA, substantia nigra; STH, subthalamic nucleus; TPP, nucleus tegmentosus pedunculopontinus; VA, nucleus ventralis anterior; VL, nucleus ventralis lateralis.

(The illustration was taken from Poirier, 1976).

the result that lesions of the area of Tsai or MFB may damage more than the nigrostriatal DA pathway (Bedard et al., 1969; Parent and Poirier, 1969; Parent, Saint-Jacques and Poirier, 1969; Poirier and Sourkes, 1965; Poirier, Singh, Boucher, Bouvier, Olivier and Larochelle, 1967; Poirier, Sourkes, Bouvier, Boucher and Carabin, 1966). Although neither the origin (Parent and Poirier, 1969; Poirier, 1971) nor the precise function of these norepinephrinergic and serotoninergic fibres is established yet, caution is advisable in the interpretation of data from experiments employing lesions of the area of Tsai or the MFB.

1:6. BRIEF REVIEW OF EXPERIMENTAL STRATEGIES ADOPTED IN THE PRESENT THESIS.

In the light of the many experimental findings referred to above it may be concluded that the integrity of the nigrostriatal DA system is indeed essential for normaly spatial, motor and ingestive behaviours. However, several questions are yet to be answered in this regard. For example, what are the precise contributions of the nigrostriatal DA system to these and other psychological functions in which it has been implicated? Might not the other systems which are frequently damaged by lesions aimed at the nigrostriatal DA system be the ones that actually regulate such functions? The present thesis reports a series of experiments designed to throw a light on these and related questions.

Lesion studies suggesting an important role for the nigrostriatal DA system in a variety of behavioural phenomena have frequently employed bilateral lesions of the nigrostriatal DA pathway. Bilateral destruction of this pathway is, however, known to produce animals that are akinetic, aphagic and adipsic, and as such very ill and inaccessible

to meaningful behavioural analysis. In view of this problem associated with bilateral nigrostriatal damage, it was judged for the purpose of this thesis to use, where lesions were applied, animals with unilateral damage; the rest of the thesis comprises psychopharmacological experiments aimed at clarifying the role of the nigrostriatal DA system in certain of the behavioural functions being investigated.

The cardinal principle governing the design of the work presented in this thesis may be described as that of tackling definite questions from a variety of angles. Thus questions of ingestive behaviour and body weight regulation (for example, food and water intake, food utilisation and motivation) were studied in terms of the effects of (a) unilateral 6-OHDA lesion of the MFB (Chapter 3), (b) unilateral kainate ablation of neuronal perikarya intrinsic to the striatum (Chapter 7), and (c) chronic haloperidol blockade of DA receptors (Chapter 6). Sensorimotor function was investigated both in its own right (see Chapters 4 and 7) and in relation to feeding (Chapter 3), using both a unilateral 6-OHDA lesion of the MFB (Chapters 3 and 4) and a unilateral kainate lesion of the striatum (Chapter 7) and employing in addition apomorphine stimulation of DA receptors (Chapter 5). Also a unilateral 6-OHDA lesion of the MFB was used in the investigation of various forms of space-related behaviour, such as spontaneous rotation (see Chapters 3, 4 and 5), lever preference in a two-lever operant behaviour situation (see Chapters 3, 4 and 5) and side preference in a T-maze (see Chapter 4); and rotational behaviour and lever preference were investigated further with the help of a unilateral kainate lesion of the striatum (see Chapter 7).

A/

A multi-dimensional approach to the questions dealt with in the present thesis seemed necessary because of the very nature of the focus of the thesis. Thus, investigating the psychophysiology of the nigrostriatal DA system is an undertaking which must contend with at least two inherent drawbacks. Firstly, no one tool is available yet to isolate the nigrostriatal DA system from the huge array of central neurochemical systems, for separate study; and, secondly, every integral aspect of behaviour that may be singled out for study is composed in turn of a conglomeration of overlapping and intermingling aspects. There is, therefore, no direct route to the goal of the enquiry.

CHAPTER 2

TECHNIQUES

2:1 HOUSING OF SUBJECTS

Throughout the experiments presented in this thesis, the subjects (ss), which were male Wistar albino rats, were housed in a reverse-daylight room where the lights regularly came on at 7.00pm and went out at 7.00 am. A reverse daylight arrangement seemed necessary because rats are known to be more active in the dark than in the light, and the animal house which supplied the rats for these experiments was open only in the day. It was aimed to observe the ss in their more active phase of the light-dark rhythm.

In experiments investigating individual feeding behaviour (see Chapters 3, 6 and 7) the ss were housed individually in R1 cages of North Kent Plastic Cages Ltd. (each R1 cage measures 38cm x 25cm x 18cm). Animals used in the other experiments (see Chapters 3, 4, 5 and 7) lived two per cage in the larger RC1 cages of North Kent Plastic Cages Ltd. (measurements 56cm x 38cm x 18cm). Photographs of the R1 and RC1 cages are shown in Figure 2.

It seemed reasonable to orientate all freshly acquired ss in the experimental housing conditions for as long as available time and other constraining factors permitted before using them in an experiment. Taking into account, therefore, the size of work designed for this thesis and the need to make the general conditions identical for all ss in all the experiments, it was decided to fix this environmental orientation period at seven days.

FIGURE 2:/

FIGURE 2:

Photograph showing the kinds of cages used for housing rats.

A: RC1 cage of North Kent Plastic Cages Ltd.

(Measurements: 56cm x 38cm x 18cm)

B: R1 cage of North Kent Plastic Cages Ltd.

(Measurements: 38cm x 25cm x 18cm)

It should be noted that the R1 cage is sitting on a tray which bears a sheet of paper for collecting rat faeces and spilled food. During experiments the cages were kept on suitably designed racks which ensured that the contents of the collecting paper on the tray could not be reached by the rat through the spaces between the metal rods of which the floor of the cage is made.

2:2 OPERANT BEHAVIOUR TRAINING AND DATA-COLLECTION.

Some of the studies presented in this thesis centered on food-rewarded lever pressing in a Skinner box. Before starting operant behaviour training the ss were deprived of food for 24hrs (in experiments in which the animals to be trained included a lesioned group) or for 48hrs (in experiments in which all the animals to be trained were unlesioned). The decision to limit specially the length of time that lesioned ss were deprived of food was dictated by the understanding that animals sustaining a lesion of the nigrostriatal system lose weight (Baez, Ahlskog and Randall, 1977) and are as such ill. Since it was by no means certain how well such animals could cope with experimentally imposed restrictions on food intake, it seemed reasonable to deprive them of food for as short a period as the requirements of the experiments permitted. The control ss used in the particular experiments were starved for an identical length of time to provide a base-line on which to evaluate any unusual observations made in respect of the lesioned animals.

All ss used in the operant behaviour experiments were trained to press a lever for food (45mg precision food pellets supplied by Campden Instruments, London) in a two-lever Skinner box having only one food-tray, which was positioned half-way between the levers. Figure 3 is a photograph of the inside of the Skinner box used. The ss were free to push on either lever; and an s received a single pellet for every push that depressed a lever.

It was considered desirable to make the conditions of training as far as possible identical for all ss. Therefore the investigator avoided/

avoided shaping the ss from outside the Skinner box. Instead a trial-and-error learning procedure entirely controlled by the ss was adopted. However, in an attempt to achieve efficient "auto-shaping", two pellets were crushed on each lever and three other pellets were placed in the food-tray before an s was introduced into the box for a training session. That way all ss were offered an equal invitation to the levers and the food-tray.

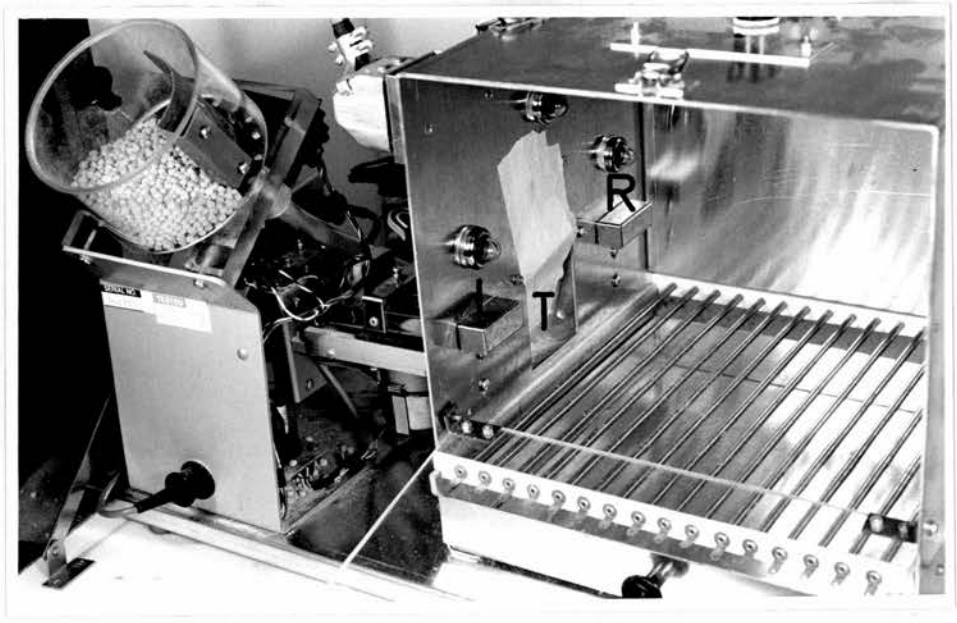


FIGURE 3:

Photograph showing the inside of the operant behaviour box used. Abbreviations: L, left lever; R, right lever; T, food-tray.

The criterion of learning was arbitrarily fixed at 20 lever presses that were each followed up immediately with the retrieval of food at the food-tray.

For all ss the initial training session lasted 60min and unless the criterion of learning was reached in that session a subsidiary 30-min session was given two hours later. Usually, normal hungry rats showed the earliest signs of learning before the end of the second training session; in fact five of the 55 ss used in the operant behaviour experiments did so during the first session. However, the training plan had a provision for any ss that would fail to learn in the first day of training; such ss, which included 12 of the 13 pre-lesioned ss (see 3:2(iii) and 4:2(c)(i)) and three unlesioned ss were given a second and, where necessary, a third day of training.

When an s reached criterion it was allowed to go on working for reward for another 30-min period before being removed from the box. The following day the s was given a further 30-min run in the Skinner box; if the animal continued to perform well this was regarded as a confirmation that it had learned and was ready for data-gathering session.

The variables observed and recorded in the data-gathering sessions were: number of effective (i.e. rewarded) lever presses executed <u>with each forepaw</u>; number of abortive (i.e. subthreshold presses made <u>with each forepaw</u>; <u>total number</u> of effective presses made in given time (rate of lever-pressing); number of effective presses made <u>on each lever</u> (lever preference); and number of rotations in each direction (left/right).

Recording of quantitative observations was carried out with the help of a manually operated multi-channel counter, each kind of observation (such as number of effective presses with the left forepaw) being recorded/

recorded on one channel. Records obtained with the manually operated device in respect of number of effective presses made on each lever, and so also in respect of total number of effective presses made, were checked against figures provided by a set of electromagnetic counters.

The recording of number of rotations in each direction was not automated because no tool was available for recording rotations without first strapping the ss across the shoulders. It was thought that binding an s across the shoulders could interfere with its lever-pressing and other activities in the Skinner box. The pattern of forepaw use, as reflected in the number of presses made with each forepaw, was also not recorded automatically because an appropriate tool for automatic recording of such variables was not available.

2:3 T-MAZE BEHAVIOUR: TRAINING AND DATA-COLLECTION

The animals used in the T-maze study (4:2(B)(ii)) were deprived of food for 48hrs just before being introduced into the training situation. Following food deprivation the ss were run in a wooden T-maze (Figure 4). The stem of the maze was 90cm long, its arms, bounded by and including the two goal-boxes, also measured 90cm from one end to the other. The passage through the maze was 15cm deep and 15cm wide throughout. The maze had a series of bilateral grooves in its walls wherein the manually operated gates fitted smoothly causing minimum noise. The roof of the maze was a wire mesh permitting observation of the s.

FIGURE 4:/

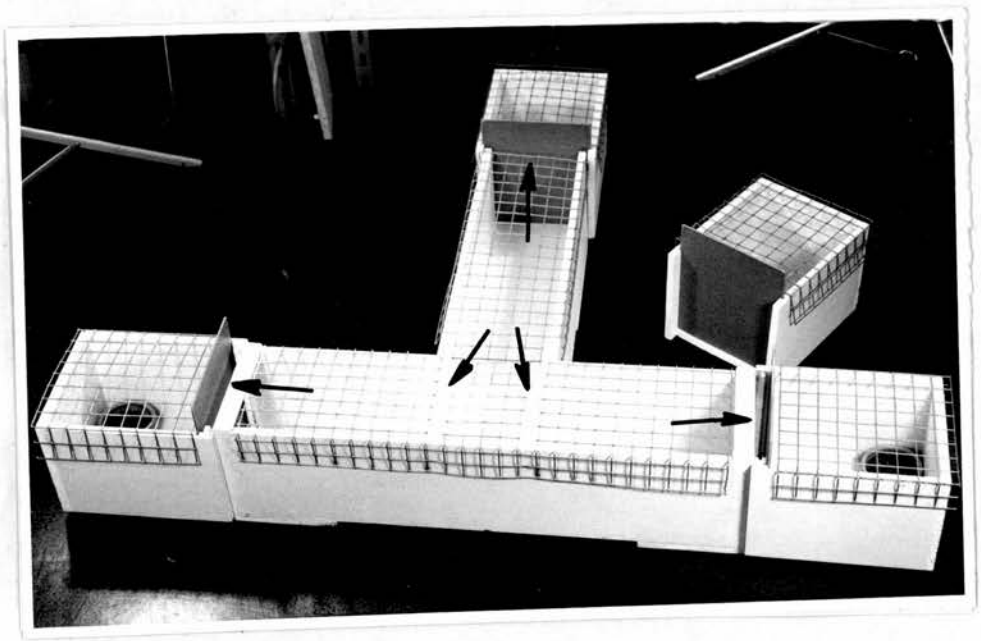


FIGURE 4:

Photograph showing the T-maze and "transit-box" used.

The arrows indicate the positions of the "sliding-doors".

The stem of the maze is 90cm long, the sides measure 90cm from one end to the other, and the passage is 15cm wide and 15cm deep throughout.

The behavioural study was initiated for every s by placing the s in the start-box of the maze after providing at each goal-box a dish of powdered food that was thoroughly mixed with a small amount of tap water. The food used was Oxoid modified 41B diet. The s was allowed to roam freely in the maze and feed for 10 minutes at either goal-box. Then the s was trapped quietly at either goal-box with the help of the manually operated sliding gates and gently picked up and placed in a transit-cage.

The entire maze was cleaned with a dry piece of cloth to remove all cues that might bias the s in favour of either arm or goal of the maze, and the dishes were thoroughly mixed and switched between the goal-boxes. These steps seem effective since side and goal preferences were random in all the ss prior to surgery. ~~(see Figures 14a and 14b).~~

Next, the s was taken from the transit box and placed back at the start-box of the maze and was allowed once more to range freely and feed for 10 minutes. This operation concluded the first day's session for every s.

The ss were given their full day's session one at a time; in other words, each s was fully run for the day before another s was started. The maze was cleaned with a wet piece of cloth and dried at the end of each rat's session to make the maze free of all traces of its presence, when the next s arrived. The policies of massed practice and regular maze-cleaning were adopted throughout the training sessions and also when data were collected before and after surgery. Furthermore, the experimenter made sure during data-collection as well as training to mix up the food supplies provided at the goal-boxes and to exchange the food-containers at the end of each single run by an s; fresh food was provided for every s in containers identical to those used for other ss.

On the second day of training, and in all subsequent sessions, each s was placed gently in the start-box after the goal boxes had been appropriately equipped with food. Thirty seconds later the start-box gate was quietly removed and the s was allowed to run to the goal-box of its choice and feed. The s was permitted to feed for 30sec and then was trapped inside an arm of the maze (usually the arm chosen by/

by the s). The s was allowed a further 30sec before being trapped further right within the chosen goal-box and being returned to the start-box via a transit box. 10 such runs constituted the second day's session for every s, except that in the tenth run the s was left trapped in the goal-box to feed for 10min undisturbed.

The final training session for an s was that in which it took, for the first time, an average of 6sec or less, from the time the start-box gate was slid open, to run the maze and commence feeding at either goal-box. Then the data-gathering sessions were due to commence.

The variables observed and recorded in the data-gathering sessions were: number of times an s chose each arm of the maze (side preference); number of times an s turned away from a goal-box and left without feeding (goal-rejections), and amount of time (in sec) taken to run the maze. A manually operated multi-channel counter was used to record the first two variables, one channel serving one definite kind of observation (e.g. number of times an s chose the right arm of the maze). Time was recorded with a stop clock.

2:4 INVESTIGATION OF FEEDING BEHAVIOUR AND BODY WEIGHT CONTROL

The setting for this category of studies was the R1 cage (see Figure 2), obtained from North Kent Plastic Cages Ltd. The design of the R1 cage permits the separate measurements of water intake, food intake, food spillage and faeces produced. The floor of the cage is composed of an array of stainless steel grids, through which spilled food and faeces passed fall on to a collecting tray and out of the animal's reach. The roof of the cage is also made of stainless steel and/

and is designed to carry a stainless steel food-hopper and an inverted 240ml glass water-bottle in such a way that the s had access to their contents.

A precise quantity (usually 100g) of Oxoid modified 41B diet was placed in the food-hopper for each s, in a clean cage equipped with a sheet of paper for collecting faeces and spilled food. Also a known quantity of water (usually 100ml) was measured into the water-bottle. Following the initial operations just outlined measurements of food missing from the food-hopper, food spilled in the process of feeding, water missing from the water-bottle, and faeces passed, and also of the animal's body weight, were taken at regular times each day. Except in the case of the final session in an experiment the recording session was rounded off by equipping a clean cage and transferring the s there in preparation for the next day's measurements. A recording session lasted approximately 1hr; during this period an s had no access to food or water.

2:5 SURGICAL PROCEDURE

All the animals that underwent surgery in the studies presented in this thesis were anaesthetized by being placed in an air-tight box through which a saturated fluothane/air mixture was circulated. When an s could no longer respond vigorously to a gentle squeeze of its hind paws it was adjudged anaesthetized and was quickly transferred to a David Kopf stereotoxic instrument, where it was firmly held and a mask fitted over its snout. The anaesthetic mixture was steadily circulated through the mask at concentrations (about 1%) necessary to keep/

keep the s anaesthetized while the operation proceeded.

The actual surgery began with a sagittal cut in the skin of the animal's head. The periostium covering a predetermined region of the skull was removed by scraping with a scalpel. A hole about 2mm in diameter was made with a dental drill, and the membranes covering the cortex were carefully removed. A stainless steel cannula attached to a microsyringe was lowered through the hole into the brain, using co-ordinates previously established with the help of a neuroanatomical atlas (Konig and Klippel, 1963) to be appropriate to the objectives of the experiment in hand. Following withdrawal of the cannula at the end of an injection the hole in the skull was covered with bone-wax, and the wound was sprayed with an antibacterial agent (polybactrin) and sutured.

2:6 MICROINJECTION OF 6-HYDROXYDOPAMINE (6-OHDA) INTO THE MEDIAL FOREBRAIN BUNDLE (MFB)

The animals receiving an intracerebral microinjection of 6-OHDA were given an intraperitoneal (i.p.) injection of desipramine (25mg/kg) and pargyline (50mg/kg) dissolved in isotonic saline (2ml/kg) 30 minutes before the central administration of the neurotoxin. Desipramine is believed to protect noradrenergic systems from the toxic action of 6-OHDA (Zigmond and Stricker, 1973) through inhibiting the neuronal NE uptake process (Fuxe and Ungerstedt, 1968; Glowinski and Axelrod, 1964); and the monoamine oxidase inhibitor pargyline appears to facilitate the destruction of dopaminergic neurons by 6-OHDA (Breese and Taylor, 1970) through decreased deamination of the neurotoxin (Breese, Chase and Kopin, 1969). Combined pretreatment with these drugs seemed worthwhile

because/

because the primary focus of the studies carried out for the purpose of the present thesis is the nigrostriatal DA system; and it was hoped that the use of these drugs would permit the selective manipulation of the nigrostriatal DA system.

A 30ga cannula was used for the microinjection of 6-OHDA into the MFB. The co-ordinates adopted were: 4.1mm behind the bregma; 1.1mm lateral to the midline, and 7.6mm below the cortical surface. 6-OHDA hydrochloride was dissolved in isotonic saline which contained 0.1mg/ml L-ascrobic acid. A single dose of 8ug of 6-OHDA in 4µl of the vehicle was administered to each s at the rate of 1µl/min, using a Hamilton syringe fixed to a motorised injecting device. After each injection 4 minutes were allowed to elapse, before the cannula was withdrawn.

Of 40 ss injected in different experiments 31 were successful, as evidencedby total or near-total loss of striatal DA on the lesion side (see Tables VIII, IX and X).

2:7 KAINATE ABLATION OF STRIATAL INTRINSIC NEURONAL PERIKAIYA

The co-ordinates used for microinjection of kainic acid into the striatum were; 0.5mm to the front of the bregma; 2.5mm lateral to the midline and 4.5mm below the cortical surface. Kainic acid was dissolved in isotonic saline and adjusted to a pH of 7.4 with sodium hydroxide. Injection was done manually with the help of a Hamilton syringe. Each s received 1.5µg of kainate in 0.3µl of isotonic saline, over a 7-min period. At the end of the injection 5min were allowed to elapse before the removal of the cannula.

Of 14 lesioned ss 13 showed no extrastriatal damage, as confirmed histologically (see 7:3:(A)(ii); and 7:3(B)(iv)).

2:8 OPERATION OF CONTROL SUBJECTS

In some of the lesion experiments presented in this thesis the experimental ss served as their own controls in that they were observed first before and then after surgery and no additional control group was used (4:2(B)and 7:2(B)). However, in some other experiments a separate unlesioned control group was also included (3:2; 4:2(A); 5:2; and 7:2(A)).

Where an unlesioned control group was employed the ss in this group were subjected to the same surgical treatment as the experimental ss in every respect except that they were injected with the bare vehicle not containing the neurotoxin administered to the experimental group. Thus in kainic acid experiments (Chapter 7) any unlesioned control ss used were given a unilateral intrastriatal administration of 0.3µl of isotonic saline not containing kainic acid. Similarly, in 6-OHDA experiments (see Chapters 3 and 4) any unlesioned control ss used were given a unilateral microinjection of 4µl of isotonic saline containing 0.1mg/ml L-ascorbic acid, and received no 6-OHDA in this vehicle solution.

In two 6-OHDA experiments (3:2 and 4:2:A) ss in which the injection cannula had not gone to the intended target served as a further control group.

2:9 DISSECTION

Animals to be sacrificed for histological and/or biochemical examination at the end of an experiment were stunned by a blow on the thorax and decapitated, and their brains were quickly removed.

Both the 6-OHDA and the kainate-lesion sets of studies involved the/

the dissection of the striatum for purposes of biochemical examination. In the 6-OHDA design the striatal sample was dissected out by making a coronal knife-cut through the brain at the middle of the optic chiasma, separating out the left and right parts of the rostral piece and then exposing the ventral aspect of the striatum by carefully removing the septum and other tissues ventral to the striatum. The striatal sample for the estimation of DA and NE was picked up with the help of a small pair of curved forceps.

The procedure for obtaining a striatal sample in the animals used in the kainate experiments was identical to that just described in all respects except that the coronal cut was made at the rostral edge instead of the middle of the optic chiasma. The striatal sample so obtained was used for the determination of CAT and GAD activities.

In both designs all non-striatal tissues between the coronal cut and the caudal end of each olfactory bulb were kept aside for the assay of DA and NE; such samples are referred to as "limbic forebrain" samples throughout this thesis.

In the kainate design, the substantia nigra on each side was also dissected out for the assay of GAD and CAT activities. The nigral sample was obtained by making a coronal knife-cut at the level of the mammillary bodies and another just 1mm behind; the substantia nigra carried in the left and right halves of the slab of tissue bounded by the coronal cuts was identified and carefully picked after a further cut just ventral and parallel to a medial lemniscus.

Also in the kainate design the block of tissue bounded by the coronal knife-cuts at the mammillary bodies and just rostral to the optic/

optic chiasma constituted the specimen for use in the histological check on damage to non-striatal tissues that might have resulted from the diffusion of kainic acid from the injection site.

In the 6-OHDA design, a random selection of ss were dissected to provide, among other things, specimen for the histological demonstration of the effect of a successful 6-OHDA lesion of the MFB on the appearance of the substantia nigra. In the selected animals a coronal knife-cut was placed at the rostral edge of the mammillary bodies and another at the rostral end of the pons to provide the block of tissue to be used for the histological work.

Figure 5a shows the levels where the knife-cuts were placed in the 6-OHDA design; the levels adopted in the kainate design are depicted in Figure 5b.

The entire process of dissection lasted between 2.5min and 4min for every s, the precise duration being determined by the number of samples required in each case.

2:10 STORAGE OF TISSUE

Following dissection, each tissue sample to be used for biochemical assay was quickly wrapped up in a piece of tin foil and stored in liquid nitrogen until time was available for it to be assayed. The blocks of tissue intended for histological study were mounted on a disc of cork and frozen quickly with the help of solid carbon dioxide and stored on ice in an air-tight container at a temperature of $-20^{\circ}C$. All assays and the cutting and staining of histological sections were done as soon after dissection as possible; the CAT and GAD assays and the preparation of histological sections were, in fact, done within 1 week, although the catecholamine assays had to wait for 4-5 weeks.

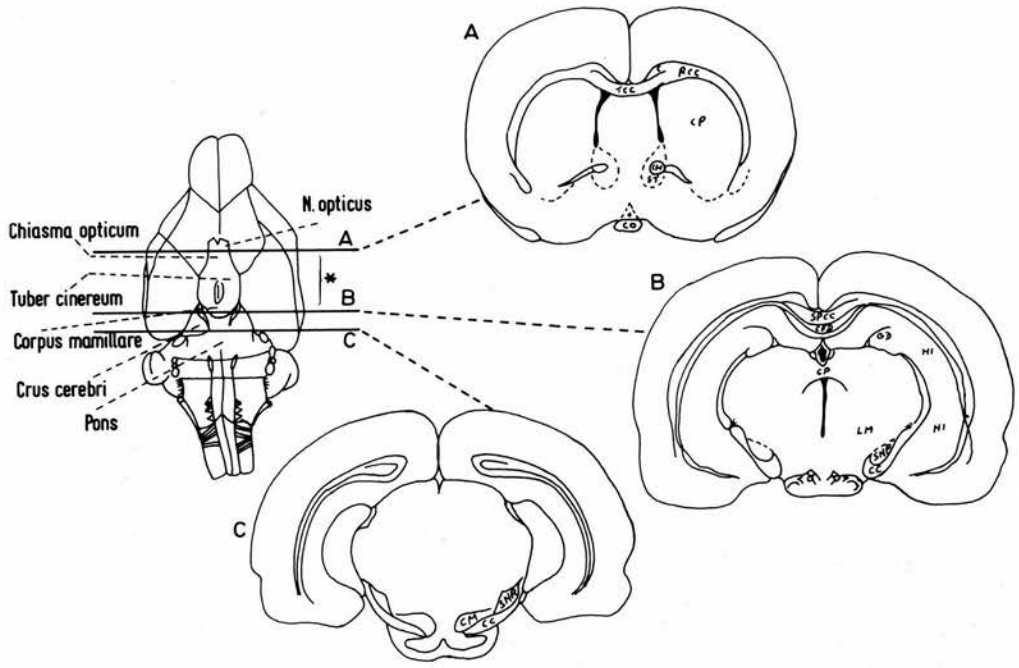


FIGURE 5a:

Schematic diagram showing the levels of coronal knife-cuts adopted in dissection in respect of animals used in the 6-OHDA experiments, *Block of tissue used for histology.

Abbreviations: C, Cingulum; CA, Commissura anterior; CC, Crus cerebri; CFD, Commissura fornicis dorsalis (Commissura hippocampi dorsalis); cm, Nucleus centre median; CO, Chiasma opticum; cp, Nucleus caudatus putamen (Striatum): CP, Commissura posterior; GD, Gyrus dentatus; Hl, Hippocampus; LM, Lemniscus medialis; RCC, Radiatio corporis callosi; SNC, Substantia nigra, zona compacta; SNR, Substantia nigra, zona reticulata; SPCC, Splenium corporis callosi; ST, Stria terminalis; TCC, Truncus corporis callosi.

(The diagrams were made with the help of illustrations in Konig and Klippel, 1963; and Zeman and Innes, 1963).

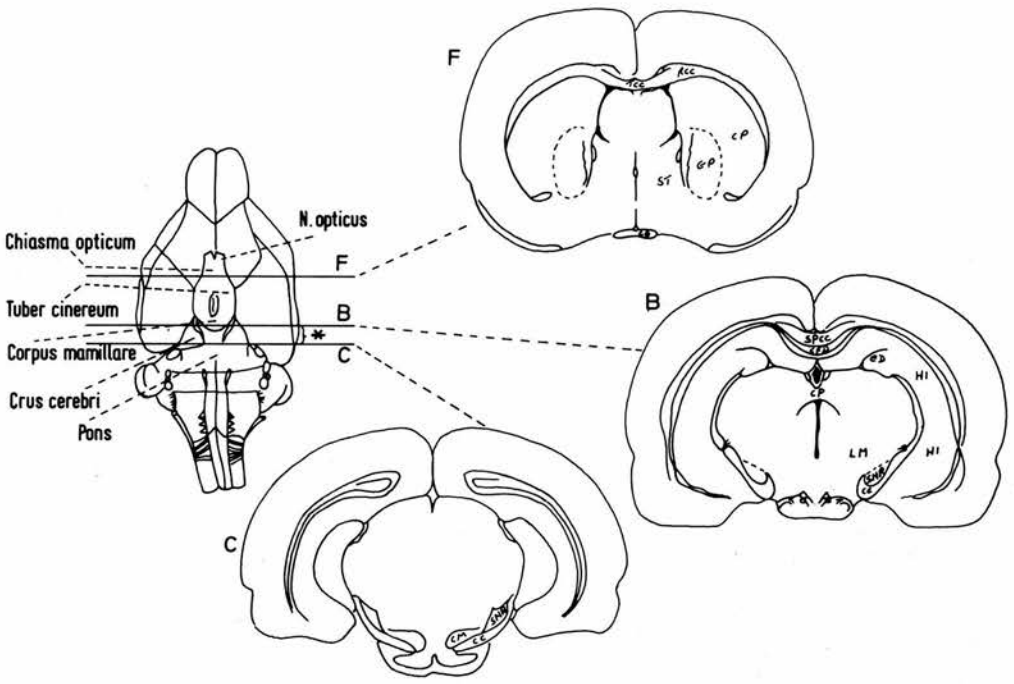


FIGURE 5b:

Schematic diagram showing the levels of coronal knife-cuts adopted in dissection in respect of animals used in the kainic acid experiments.

*Block of tissue used for histology.

Abbreviations: CC, Crus cerebri; CFD, Commissura fornicis dorsalis (Commissura hippocampi dorsalis): CM, Nucleus centre median; CO, Chiasma opticum; cp, Nucleus caudatus putamen (Striatum); CP, Commissura posterior; GD, Gyrus dentatus; GP, Globus pallidus (Pallidum; Hl, Hippocampus; LM, Lemnisus medialis; RCC, Radiatio corporis callosi; SNC, Substantia nigra, zona compacta; SNR, Substantia nigra, zona reticulata; SPCC, Splenium corporis callosi; ST, Stria terminalis; TCC, Truncus corporis callosi.

(The diagrams were made with the help of illustrations in Konig and Klippel, 1963; and Zeman and Innes, 1963).

2:11 HISTOLOGICAL PROCEDURE

Histological sections were prepared by a modification of the method of Kluver and Barrera (1953). Sections were cut at 20 microns at a temperature of -20°C, using a cryostat. One in every five sections was picked for staining and placed on a microscope slide. The sections were immersed in 95% alcohol for 5 min. To stain the fibres the sections were then immersed for 30 min in Luxol Fast Blue - 0.1% solution of Luxol fast blue (BDH Chemicals Ltd., Poole, England). This solution was prepared by dissolving 1 gram of the substance in 1 litre of 95% alcohol, and filtering after the addition of 10% acetic acid in the concentration of 5ml of 10% acetic acid per litre of 95% alcohol. After washing in distilled water by dipping a few times, differentiation was initiated by immersing in 0.05% lithium carbonate for 1 min and then in 70% alcohol for 5 min, and was completed by alternating between lithium carbonate and 70% alcohol until there was a sharp contrast between the greenish-blue colour of the white matter and the colourless gray matter. The sections were washed thoroughly in distilled water by dipping for 2 min. To stain the gray matter the sections were immersed for 4 min in cresyl violet (0.1% aqueous solution of cresyl violet). Differentiation was achieved by immersing in 95% alcohol for 5 min. After further immersion in absolute alcohol (5min), the sections were placed in xylene for at least 5min before mounting. The sections were mounted with DPX, carefully covered with a cover-slide and examined under a light microscope.

2:12 RADIOENZYMATIC ASSAY OF DA AND NE.

DA and NE were measured by the radioenzymatic method of Coyle

and/

and Henry (1973) and Palkovitz, Brownstein, Saavedra and Axelrod (1974). The tissues were homogenized in 0.1N perchloric acid (PCA) - 5mg of striatal tissue or 50mg of limbic forebrain tissue in 300µl of PCA. After centrifuging at 10,000 x g for 15min, 300ul aliquots of the supernatant were placed in 15ml glass-stoppered centrifuge tubes. Standards consisted of 25ng (free base) of DA and NE in 300µl of PCA; and 300µl aliquots of brain extract and 300ul of PCA constituted the blanks. The tissue samples, standards and blanks, were set up in duplicates for the purpose of the assay.

The incubation mixture consisted of 500mg of dithiothreitol; 0.5 µ moles of $MgCl_2$; 40 µ moles of Tris-HCl buffer, pH9.6; 25µl catechol - O-methyltransferase; and 2.5ul of ^3H methyl-S-adenosyl-methionine. Catechol-O-methyltransferase was prepared from rat liver by the method of Coyle and Henry, (1973). 100µl of the incubation mixture were added to each tube. Incubation was for 60min at 37°C. The reaction was stopped by adding 500µl of 0.5M borate buffer pH10. 50µl of a nonradioactive carrier solution containing 7µg of methoxytyramine, 3ug of normetanephrine, 3µg of metanephine and 1mg of EDTA were added to each tube. The O-methylated products were extracted into 9mls of water-saturated ethyl acetate-methanol (10:1 v/v) by shaking manually for 30 sec. The phases were separated by centrifuging at low speed and 8.5mls of the organic phase were transferred to another tube containing 500ul of 0.5M borate buffer, pH 10. After again shaking for 30sec and centrifuging 8ml of the organic phase were transferred to a third tube containing 500µl of 0.1N HCL. The O-methylated products were extracted into the aqueous phase by shaking for 30 sec. Following centrifugation

at/

at low speed for 5min the organic phase was removed by aspiration. The acid phase was washed with an additional 8ml of water-saturated ethyl acetate by shaking for 30 sec. After centrifugation the ethyl acetate was aspirated off.

500µl of 0.5 M sodium phosphate buffer (pH7.5) were added to each tube and the tubes were transferred to an ice bath. To separate DA from NE, the side-chain of NE was cleaved at the beta-hydroxyl position with 50µl of freshly prepared 3% (W/V) sodium metaperiodate. The reaction was allowed to continue for precisely 3min and was stopped by the addition of 50µl of 10% (v/v) glycerol. The ^{3}H methyl-vanillin was extracted into 10ml of toluene by shaking for 30 sec. After centrifugation 9ml of the organic phase were transferred to another tube containing 1ml of IN NaOH. The aqueous phase remaining after the transfer of 9ml of toluene was kept aside for the determination of DA.

The tubes containing IN NaOH and toluene were shaken for 30sec and after centrifugation the organic phase was aspirated off. The aqueous phase containing the ^{3}H methyl-vanillin was acidified with 0.1ml of glacial acetic acid. 10ml of toluene were added to each tube and the tubes were shaken for 30 sec. After centrifuging, 9ml of the organic phase were transferred to a counting vial containing 0.4ml of Liquifluor (New England Nuclear Corporation) and counted in a scintillation counter.

To determine DA, 5ml of toluene were added to each one of the tubes containing the aqueous phase of the sodium metaperiodate cleavage reaction. The tubes were shaken for 30sec and after centrifugation the organic phase was aspirated off. 500µl of IM borate buffer, pH11 and/

and 6ml of toluene-isoamyl alcohol (3:2, v/v) were added to each tube. The ^{3}H methyl-methoxytyramine was extracted into the organic phase by shaking for 30sec. After centrifugation 5ml of the organic phase were transferred to a counting vial and counted in 10ml of NE 260 scintillant in a scintillation counter.

This assay method is known to have a sensitivity of at least 0.2ng for DA and 0.1ng for NE in 300µl of homogenate, and to exhibit linearity for amounts of catecholamine ranging from less than 1ng to at least 30ng (Coyle and Henry, 1973).

2:13 DETERMINATION OF CHOLINE ACETYLTRANSFERASE (CAT) ACTIVITY

CAT activity was determined by a modification of the method of Fonnum (1975), which essentially consists in measuring the labelled acetylcholine formed from L-^{14}C-acetyl-Co A and excess choline by an activated tissue preparation at a pH of 7.4 in the presence of eserine and a high concentration of sodium chloride. The labelled acetylcholine was separated from the substrate by binding to tetraphenylboronin, the organic phase of a two-phase solvent system. The labelled substrate remained uncounted in the acqueous phase.

The tissues were homogenised in a homogenisation buffer consisting of 1mM EDTA, pH 7.0, containing 1ul Triton X-100/ml-1mg of tissue in 50µl of buffer. The homogenates so obtained were diluted ten times with the homogenisation buffer to make a 0.2% concentration, and were stored in ice.

The incubation mixture was prepared on ice and contained:

100mM	EDTA pH 7.4
200mM	Choline Chloride

3.0M/

3.0M	NaCL
0.5M	NaH_2PO_4 buffer pH 7.4
2 mM	Eserine salicyclate
9mg/ml	Bovine Serum Albumin
2mM	Acetyl (1-C^{14}) CoA

To 10µl of the incubation mixture were added 10µl of the homogenate in an uncapped Eppendorf tube. Incubation was carried out in an Eppendorf dri-block at 37°C and lasted 20min.

The blanks were 10µl of the homogenisation buffer.

To stop the reaction the Eppendorf tubes were removed from the dri-block and placed into scintillation vials containing 2ml Kalignost/acetonitrile[a], 5ml 10 mM NaH_2PO_4 + acetycholine[b] and 10ml scintillant[c]. The vials were stoppered firmly and the ingredients mixed well - but gently, to ensure a clean separation of the two phases. The vials were placed in a scintillation counter immediately after this step, and were left for 1hr and then counted for 4min.

Samples and blanks were analysed in duplicate.

In this assay procedure, the reaction is linear for 20min for a 0.2% homogenate of rat brains.

Notes:

a. Kalignost/acetonitrile: For ten assays 186.9mg Kalignost (sodium tetraphenylboron - Sigma Company) were added to 20ml acetonitrile.

b. 10 mM NaH_2PO_4 + acetylcholine: 780mg $NaH_2PO_4 2H_2O$ were dissolved in 450ml water and 18mg unlabelled acetylcholine chloride. The pH was adjusted to pH7.4 with 1 M N_aOH and the volume was made up to 500ml with water.

c. Scintillant: 8.5g PPO were added to 2 litres toluene.

2:14 DETERMINATION OF GLUTAMIC ACID DECARBOXYLASE (GAD) ACTIVITY

GAD activity was determined by measuring the rate of formation of $^{14}CO_2$ from L-^{14}C glutamic acid on incubation with a tissue homogenate in the presence of pyridoxal phosphate. The method used was a combination of the methods of Drummond and Phillips (1974) and Urquhart, Perry, Hansen and Kennedy (1975).

The tissues were homogenised in a homogenisation buffer prepared by adding 100µl of 10% Triton X-100 and 100ul of 10mM pyridoxal phosphate to 10mls of 1mM K PO_4 buffer pH6.5.1mg of tissue was homogenised in 20µl of homogenisation buffer.

The incubation mixture contained:

100 mM	KPO_4 Buffer pH6.5
10 mM	Sodium Glutamate
1 mM	Sodium Arsenite
0.5 mM	Pyridoxal Phosphate
0.5 mM	Dithiothreitol
0.01%	Triton X-100
0.045 mM	L-^{14}C Glutamate

An insert vial containing an Eppendorf tube was placed in a scintillation vial which contained 250µl protozol. Into the Eppendorf tube were added 10µl of the homogenate and 10µl of the incubation mixture, and the scintillation vial was stoppered with a rubber seal. Incubation was done at 37°C and lasted 20 min.

To stop the reaction 100ul 6N H_2SO_4 were injected through the rubber seal. The scintillation vial was left for 60min at 37°C to collect $^{14}CO_2$. Two millitres of ethanol were used to wash the outside of/

of the insert vials. After the seal and the insert vial containing the Eppendorf tube were removed 10ml of toluene scintillant were added. The scintillation vial was then placed in a scintillation counter and counted for 10 minutes.

CHAPTER 3

AN INVESTIGATION OF THE INVOLVEMENT OF THE NIGROSTRIATAL DOPAMINE SYSTEM IN FEEDING, SENSORIMOTOR FUNCTION, MOTIVATION, ROTATIONAL BEHAVIOUR AND LEARNING

3:1 INTRODUCTION

3:1(i) FEEDING AND DRINKING AND BODY WEIGHT CONTROL FOLLOWING NIGROSTRIATAL DAMAGE.

Although a detailed analysis of the nature of nigrostriatal dopaminergic involvement in ingestive behaviour and body weight regulation has not been published, it is known that these functions are seriously disrupted following nigrostriatal damage.

Bilateral lesions which interrupt the nigrostriatal DA pathway in rats produce aphagia and adipsia in the acute phase and also a constellation of long-term regulatory deficits appertaining to eating and drinking (Fibiger, Zis and McGeer, 1973a; 1973b; Marshall and Teitelbaum, 1973; Ungerstedt, 1971a; Zigmond and Striker, 1972). Animals with such lesions exhibit marked weight loss during the early postoperative days (Marshall et al., 1974; Oltmans and Harvey, 1976; Ungerstedt, 1971a), and thereafter maintain their weights at levels lower than those of unlesioned controls (Boyle and Keesey, 1975, Powley and Keesey, 1970). The weight deficit in the lesioned animals appears to be a phenomenon that can be explained in terms of their refusal to eat and drink in the early postoperative days (Marshall et al., 1974; Oltmans and Harvey, 1976) and their subsequent adoption of a subnormal "set-point" or target for body weight (Boyle and Keesey, 1975; Powley and Keesey, 1970).

It has been shown that a unilateral electrolytic lesion of the substantia/

substantia nigra produces short-term impairments in food and water intake (Fibiger, Philips and Clouston, 1973). In the same experiment Fibiger and co-workers failed, however, to cause deficits in ad libitum food and water intake through unilateral 6-OHDA microinjection into the substantia nigra of another group of rats. More recently, Baez, Ahlskog and Randall (1977) have observed severe weight loss following a unilateral nigrostriatal lesion which was induced by administering 6-OHDA directly into the MFB. Baez and collaborators proposed that the weight loss displayed by their rats after unilateral 6-OHDA disruption of the nigrostriatal pathway was associated with impairments in food intake; but they did not directly measure this.

Since body weight depends in part upon food and water intake, it is no surprise that the body weight deficit displayed by animals sustaining an extensive lesion of the nigrostriatal DA system is supposed to be related to lesion-induced deficits in food and water intake. But why do such animals eat and drink less than normal?

Rats sustaining bilateral lesions of the LH are known to be highly finicky about the taste of food or water. Such animals refuse food or water containing quinine at concentrations acceptable to controls (Teitelbaum and Epstein, 1962). In a study comparing the behavioural effects of nigrostriatal and LH lesions, however, Marshall, Richardson and Teitelbaum (1974) found no consistent enhancement of finickiness by nigrostriatal damage. This latter finding suggests that the ingestive and body weight deficits associated with nigrostriatal damage are not due to a disruption of gustatory mechanisms. Of interest in this regard is the fact that lesions of the thalamic and cortical areas concerned with taste have not been associated with aphagia and adipsia (Oakley and Benjamin, 1966).

3:1(ii) SENSORIMOTOR DEFICITS FOLLOWING NIGROSTRIATAL DAMAGE.

Bilateral nigrostriatal lesions cause akinesia (Fibiger, Zis and McGeer, 1973a; 1973b; Oltmans and Harvey, 1972; Ungerstedt, 1971a; Zigmond and Stricker, 1972). Also unilateral damage renders an animal incapable of orienting to stimuli applied to the side opposite to the side of lesion (Marshall et al., 1974). Furthermore, there are strong indications that the nigrostriatal system is part of a lateralised system for sensorimotor control of the limbs. For example, animals with a unilateral nigrostriatal lesion display impairments in using the contralateral limbs to resist gravitational pull (Marshall et al., 1974), and unilateral electrolytic destruction of the striatum has been shown to produce loss of the capacity to use the contralateral forepaw in lever-pressing for food in an operant behaviour situation (Hansing et al., 1968). In view of such findings as these it is not really a far-fetched notion that at least part of the impairment of feeding and drinking observed in animals with nigrostriatal damage may be due to lesion-induced sensorimotor dysfunction. What is called for is a direct experimental test of the idea.

3:1(iii) NIGROSTRIATAL DAMAGE AND MOTIVATION

Central dopaminergic mechanisms have not hitherto been implicated directly to any significant extent in the motivational aspects of behaviour. This is probably because the research designs employed in most studies concerned with dopaminergic control of behaviour involving motivational and sensorimotor elements simultaneously have often failed to permit any motivational elements in the results to be prised out/

out of the overwhelming sensorimotor observations. Thus, for example, rats given bilateral lesions of the nigrostriatal DA system become completely aphagic and adipsic and are known to be akinetic also; so that it is not possible to be sure whether or not their refusal to eat and drink is associated with loss of motivation.

The report that rats would operate a lever to stimulate their own striata electrically but would cease to exhibit this response following the destruction of the nigrostriatal DA system (Phillips, Carter and Fibiger, 1976) does, however, suggest that the nigrostriatal DA system is part of the reward mechanisms of the brain. In this regard it is interesting to note that DA receptor blockers reduce electrical self-stimulation of the brain (Dreese, 1966; Yokel and Wise, 1975), and that this effect is not due to a general depression of operant responding following treatment with such drugs (Fouriezos and Wise, 1976; Rolls, Kelly and Shaw, 1974).

Furthermore, it has been proposed that the basic deficit suffered by animals with bilateral lesions which disrupt the central catecholamine (CA) systems is in arousal (Stricker and Zigmond, 1976). In other words, brain catecholaminergic mechanisms may be involved in central arousal and motivated behaviour. Stricker and Zigmond suggest that the threshold for arousal to motivated behaviour, such as feeding, is higher in animals sustaining extensive damage to central catecholamine neurons than in normal animals.

3:1(iv) THE NIGROSTRIATAL DOPAMINE SYSTEM AND ROTATIONAL BEHAVIOUR

Asymmetry between the nigrostriatal DA systems of the two hemispheres causes rotation in the direction opposite to the more active nigrostriatal/

nigrostriatal system, whether asymmetry is produced by unilateral electrical stimulation (Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1970; Zimmerberg and Glick, 1975) or by unilateral damage (Anden et al., 1966; Christie and Crow, 1971; Ungerstedt and Arbuthnott, 1970; Ungerstedt, 1971e). Studies using a combination of unilateral interruption of the nigrostriatal pathway and systemic administration of amphetamine or apomorphine have further established that increased neostriatal DA receptor activity in one hemisphere leads to circling in the direction opposite to the more active striatum (Ungerstedt, 1971c; 1971e). Moreover, it has been shown that amphetamine increases the asymmetry in DA content between the two striata (Glick, Jerussi, Walters and Green, 1974) and elicits circling in the direction opposite to the striatum with the greater DA (Glick, 1973; Glick and Jerussi, 1974; Glick, Cox and Greenstein, 1975).

A large unilateral electrolytic lesion of the locus coeruleus, which does not actually interrupt the nigrostriatal pathway, has, however, been shown to be associated with strong, though transient, contraversive rotation when the lesioned animals are given a systemic injection of amphetamine or apomorphine (Donaldson, Dolphine, Jenner, Marsden and Pycock, 1976; Pycock, Donaldson and Marsden, 1976). What is interesting about these latter studies is that an elevation of DA levels was observed in the ipsilateral striatum and this would appear to support the view that the circling behaviour observed was related to an asymmetry in DA receptor stimulation. In fact that was exactly the conclusion reached by the authors following further work.

3:1(v) IMPAIRMENT OF LEARNING FOLLOWING NIGROSTRIATAL DAMAGE

There are several reports that central 6-OHDA administration disrupts the capacity to acquire a conditioned avoidance response (for example, Cooper, Breese, Howard and Grant, 1972; Fibiger, Phillips and Zis, 1974). It has been suggested that the apparent inability of 6-OHDA lesioned animals to acquire such a response reflects an impairment of their ability to initiate voluntary movements (Price and Fibiger, 1975; Smith, Levin and Ervin, 1975) rather than any basic disruption of learning capacity. Ranje and Ungerstedt (1977) have, however, shown that rats with extensive 6-OHDA-induced damage of the nigrostriatal DA systems of both hemispheres are "unable to acquire a brightness or spatial discrimination task even when the experimental situation is such that they are able to overcome their difficulties to initiate voluntary movements". Ranje and Ungerstedt's results strongly suggest that the integrity of the nigrostriatal DA system is essential for the acquisition of certain kinds of learning.

3:1(vi) EXPERIMENTAL DESIGN AND RATIONALE.

In the design of the present study the experimental group of ss were to be given a unilateral 6-OHDA-induced lesion of the nigrostriatal DA system. Unilateral damage was considered preferable to bilateral damage because the multitude of already published studies which have used bilaterally lesioned animals provide compelling evidence that bilateral damage yields preparations which in at least the early postoperative phase are hardly accessible to meaningful behavioural analysis. Rats intended to serve as controls received a microinjection of the bare vehicle solution, or were injected with 6-OHDA at co-ordinates that were sure to miss the nigrostriatal DA system.

The study was designed primarily to tackle questions appertaining to the precise nature of the weight loss and related phenomena associated with 6-OHDA-induced degeneration of the nigrostriatal DA system, and secondarily to investigate the effect of such a lesion on operant learning, forelimb use and rotational behaviour. The specific questions dealt with include the following:

(a) Do rats with a unilateral lesion of the nigrostriatal DA system display a deficit in body weight?

(b) Do they eat and drink less than controls?

(c) Are any observed ingestive deficits due to sensorimotor dysfunction?

(d) Is there an impairment of motivation?

(e) Do lesioned animals suffer a metabolic impairment which may be reflected in the amount of faeces produced per unit amount of food ingested?

(f) Does a unilateral nigrostriatal lesion impair an animal's capacity to learn an operant task?

(g) Does such a lesion produce a consistent preference of one or the other forepaw in food-rewarded lever pressing?

(h) Does it enhance spontaneous rotation?

(i) Does it produce a consistent preference for one or the other direction of circling?

Questions (a)-(e) were approached by taking regular daily measurements of each rat's body weight, food and water intake, food spillage and production of faeces, under conditions of virtually uninterrupted food and water supply. Measurements of body weight, food and water intake and food spillage were also taken (i) following

a/

a period of food deprivation and (ii) following a period of water deprivation.

Obviously, if reduced food intake is responsible for the deficit in body weight observed in rats with a unilateral nigrostriatal lesion (Baez et al., 1977), such animals would consume significantly less food than controls under conditions of ad lib. food availability, and possibly also following food deprivation. It was predicted furthermore that if sensorimotor dysfunction was responsible even in part for the feeding deficit, or if at any rate a sensorimotor impairment of some kind of relevance to feeding resulted from unilateral nigrostriatal damage, such a sensorimotor impairment should manifest in some degree in the food-spillage habits of the animal. In this regard it may be recalled that bilateral pallidal lesions, which, like nigrostriatal lesions, produce feeding and body weight deficits, have been shown to be associated with an impairment in the capacity to use the musculature of the mouth region (Levine and Schwartzbaum, 1973). It has been proposed, moreover, that in at least one parameter, that of body weight, unilateral nigrostriatal damage is as disruptive as bilateral damage (Baez et al., 1977). It seemed promising therefore in the present study to look for evidence of sensorimotor impairment in the food-spillage habits of animals with a unilateral lesion of the nigrostriatal system.

Partly to check more directly on the possibility of the existence of sensorimotor dysfunction in animals with unilateral nigrostriatal damage (Question (g)), the animals used in the present study were also trained to push a lever for food reward in a Skinner box. The animals were permitted to use the forepaw of their choice for lever pressing, and/

and it was predicted that like animals sustaining a unilateral lesion of the striatum (Hansing et al., 1968), pallidum (Levine et al., 1971) and entopeduncular nucleus (Levine and Schwartzbaum, 1973), the lesioned rats in the present study would display a preference for the ipsilateral forepaw.

For its part motivation has been viewed in this study absolutely as a generalized state of the organism. It was therefore assumed that if the nigrostriatal system is part of an integrated mechanism controlling motivation and if bilateral nigrostriatal damage does indeed disrupt this function, some degree of disruption of the function should also be apparent following a unilateral lesion. On the basis of this assumption it was predicted that the lesioned animals in the present experiment would ingest significantly less food than controls under conditions of free access to food and following food deprivation.

It was hoped through collecting and analysing data on food intake and food spillage to ascertain whether any ingestive deficits that might be observed in 6-OHDA-lesioned animals reflected a sensorimotor or motivational impairment. Thus if lesioned animals spilled just as much food as controls and at the same time ate less, this could reflect a motivational deficit. On the other hand, if they ingested just as much food as controls and spilled more, this might mean that their impairment was sensorimotor and not at all motivational. Of course, lesioned animals might turn out to both eat less and spill more, in which case their handicap could be interpreted as having both motivational and sensorimotor aspects.

In the part of the study set in the Skinner box the process of learning (Question (f)), and rotational behaviour (Questions (h) and (i)), were observed in addition to patterns of forelimb use.

All/

All the animals were killed shortly after the study in order to estimate the extent of brain damage suffered by the lesioned group as compared to controls. To this end, DA and NE were assayed in striatal and limbic forebrain samples (see 2:12) to determine the amount of damage done to the nigrostriatal DA system and the amount of spread of the lesion to other catecholaminergic systems supplying the forebrain.

3:2 MATERIALS AND METHODS

3:2(i) SUBJECTS

The ss were 17 male Wistar albino rats weighing between 170g and 200g at the time of surgery.

On arrival in the laboratory the animals were placed on a reverse daylight schedule as previously described (2:1).

For the parts of the study concerned with the investigation of feeding behaviour per se the animals were housed singly in R1 cages of North Kent Plastic Cages Ltd. (measurements: 38cm x 25cm x 18cm) which permitted the separate measurements of food and water intake, food-spillage and faeces.

For the part of the study which consisted in observing the ss in an operant behaviour situation for sensorimotor performance (forepaw use) and rotational behaviour, the animals were housed in twos in standard RC1 cages of North Kent Plastic Cages Ltd. (measurements: 56cm x 38cm x 18cm). Descriptions of R1 and RC1 cages were given, with photographs, in an earlier chapter (2:1).

Throughout the investigation the ss had food and water ad libitum except that they were deprived of food or water for a predetermined period of time when their reactions and response to food- or water-deprivation were to be observed (3:2(ii)) or when their behaviour in an operant behaviour situation was the object of study 3:2(iii).

3:2(ii) PREOPERATIVE AND POSTOPERATIVE FEEDING AND BODY WEIGHT

On arrival in the laboratory the animals were housed in the R1 cage in reverse daylight for an orientation period of seven days, as previously described (2:1). Following this environmental orientation the actual investigational operations were begun by providing known quantities of Oxoid modified 41B diet and water for each s. Thereafter measurements of food missing from the food-hopper, food spilled, water missing from the water-bottle, faeces produced, and the animal's body weight were taken at regular times each day. A more detailed account of the general data-gathering procedure has been given elsewhere (2:4).

The ss were observed for seven days in the fashion described, and then taken to the theatre for surgical operation. Surgery was completed for all ss within four hours after recorded measurements were taken for the seventh day. Food and water were restored at the end of surgery and the ss were left for 16-20hrs to recover from the trauma of surgery.

The period of 16-20hrs was arbitrarily fixed, as it is not known precisely how long the acute trauma of surgery lasts. No records were taken during the so-called recovery period.

The early postoperative phase of data-gathering observation began with the preparation of the cage and the provision of food and water in exactly the same manner as before surgery. The first postoperative records were taken 44hrs after the completion of surgery.

The early postoperative phase of data collection comprised a fortnight of routine daily measurements of food and water consumption, food spillage, faeces production and body weight. When the measurements were completed for the 14th postoperative day, the ss were deprived of food for 24hrs and weight loss was determined. Then food was restored.

Twenty-four/

Twenty-four hours after food-restoration a full data-gathering session was carried out and included as usual measurements of food and water intake, food spillage and faeces as well as body weight.

At this point the ss were transferred from the R1 cages to RC1 cages, where they were housed in twos until the completion of the proposed investigation of forepaw use and rotational behaviour (3:2(iii)).

Following the latter experiment (3:2(iii)), which was carried out in the 13th postoperative week, five experimental and six control ss that had yielded the data for that study (see 3:3) were returned to the R1 individual cages. They were allowed seven days of reorientation in the R1 cage situation before recorded observation was resumed (the late postoperative phase). The late postoperative phase lasted seven days and consisted of regular daily measurements of food and water intake, food spillage and faeces. Body weight was not measured as the whole aim of this part of the study was to ascertain whether or not high food-spillage, which had been regarded tentatively as indicative of sensorimotor dysfunction, was still evident in the lesioned animals so that food spillage habits might be compared with any sensorimotor observation made in the operant behaviour situation.

3:2(iii) OPERANT LEARNING, FOREPAW USE AND ROTATIONAL BEHAVIOUR IN THE LATE POSTOPERATIVE PHASE

When the ss were removed from the R1 cages at the end of the early postoperative investigations of feeding and body weight (3:2(ii)) they remained housed in twos in RC1 cages for 10wks. The commencement of this study was delayed for so long in order that the results might be fruitfully compared to results from certain other experiments reported later (4:3(A) and 4:3(C)) in which the patterns of forepaw use by similarly operated ss were last observed two or at most eight weeks after surgery.

In the actual procedure in the present study, the ss were deprived of food for 24hrs, after which they were subjected to an operant behaviour training procedure in a Skinner box as previously described (2:2).

Animals failing to reach the criterion of learning (2:2) after three consecutive days of full-scale training operations were discarded as far as this part of the study was concerned although they were still analysed for the previous part of the study (3:2(ii)). Animals reaching criterion in the present experiment in time (i.e. within three days) were given one data-gathering session of 20min, 24hrs after the confirmation of their learning. Variables recorded included; number of effective (i.e. rewarded) lever presses executed with each forepaw, number of abortive (i.e. subthreshold) presses made with each forepaw, total number of effective lever presses, number of times each lever was operated, and number of times an s rotated toward or away from the side of the brain that had been injected at surgery. A manually operated many-channelled counter was used for recording all quantitative observations - one channel serving one distinct class of observations, such as left forepaw presses on the left lever or rightward rotations. Electromagnetic counters (Campden Instruments, London) connected to the levers provided a means of checking on the records obtained with the help of the manually operated counting device in respect of number of effective presses on each lever.

3:2(iv) SURGERY

A detailed description of the surgical procedure has been given in the chapter on techniques (2:5). Eleven proposed experimental ss were given a microinjection of 8ug of 6-OHDA into the left MFB whereas six control ss received only the vehicle (4ul of isotonic saline containing 0.1%/

0.1% of L-ascorbic acid, w/v). At the end of each injection a period of four min was allowed to elapse before the cannula was removed, the hole in the skull covered and the wound dressed and sutured.

3:2(v) VERIFICATION OF LESION

All the ss were killed within seven days after the end of the late postoperative investigation of ingestive behaviour and body weight regulation (3:2(ii)). Four brain tissue samples were dissected out from the brain of each s, as follows: left striatum, right striatum, left limbic forebrain and right limbic forebrain. The samples were assayed for DA and NE contents according to the radioenzymatic method of Coyle and Henry, (1973) and Palkovitz et al., (1973). For details of the dissection and assay procedures see 2:9 and 2:12 respectively.

3:2(vi) HISTOLOGY

It was not deemed necessary to carry out for every s a histological check on the extent of retrograde degeneration of the DA cells in the substantia nigra following 6-OHDA or vehicle injection into the MFB, as the amine assay was judged adequate for the present study. However, a random selection of three experimental and three control ss were set aside, out of those successfully used in both the feeding and sensori-motor behaviour parts of the study, in order to demonstrate histologically the appearance of the substantia nigra following 6-OHDA microinjection into the MFB.

3:3 RESULTS/

3:3 RESULTS

3:3(i) FEEDING BEHAVIOUR AND BODY WEIGHT REGULATION

Owing to irregularities in the measurement of water intake in this experiment the data collected in respect of this aspect of ingestive behaviour are not presented. However, observations relating to body weight, food intake, food spillage and faeces were carefully made, and the results are presented here.

Eight ss sustaining an extensive lesion of the nigrostriatal DA bundle, as confirmed by catecholamine assay results, displayed dramatic changes in their feeding behaviour and body weight regulation. The 3 partially lesioned ss and the 6 control ss, on the other hand, did not exhibit any observable modification of their feeding behaviour or their body weight control. For the purpose of the presentation of the results from the study, therefore, the partially lesioned ss are considered along with the controls to form a control group of 9 ss, the 8 successfully lesioned ss constituting the experimental group.

The results are presented for the most part in terms of records taken over periods of seven days as follows: one week before surgery, first postoperative week, second postoperative week and one week in the late postoperative phase (i.e. three months after surgery). However, acute effects of surgery, and the animals' reactions and responses to food deprivation as well, are presented from a single day's record.

As Figure 6 shows the body weights of the experimental and control groups of ss (measured in grams) were similar before surgery, but following/

following surgery the experimental group suffered a drop in body weight which was sustained; these ss did not manage to catch up again with the control group while the observation period lasted. Table I shows the mean increase in body weight displayed by the two subject groups over periods of seven days just before and for two weeks after surgery. Statistical treatment of the data using the Mann-Whitney U test revealed no significant difference between the two groups before surgery. On the other hand, a similar statistical treatment of the postoperative data showed that the experimental ss gained a significantly smaller amount of weight than the control ss during the first postoperative week ($p < 0.001$, one-tailed test), and also during the second postoperative week ($p < 0.01$, one-tailed test).

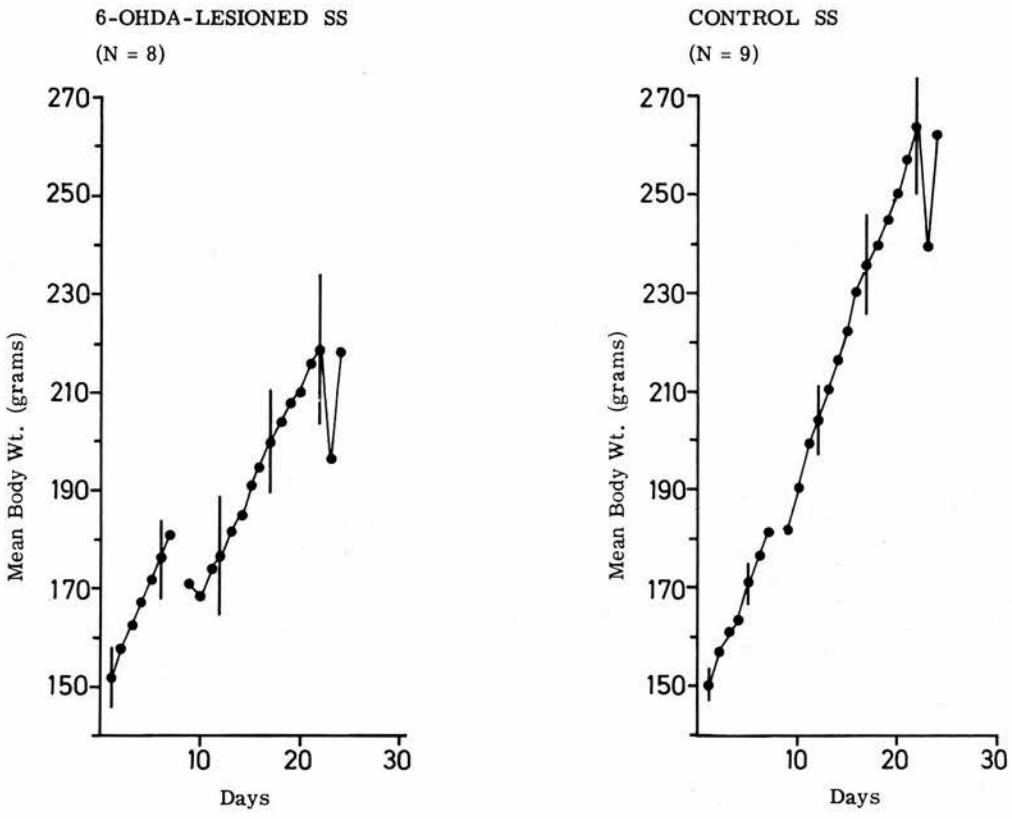


FIGURE 6:

Mean body weights displayed from day to day by rats with a unilateral 6-OHDA-induced lesion of the nigrostriatal system and by controls.

The two groups of ss were similar in mean body weights prior to surgery; but for 3 days after surgery the experimental group suffered a steady loss of weight and thereafter remained underweight relative to the control group.

The bars represent the standard deviations (SD) on the days indicated. The SDs were computed for each day of the study; but, for the sake of clarity only a few are shown in the graph.

Periods	Experimental Group of Ss (N=8)	Control Group of Ss (N=9)
Immediate Preoperative Week	29 $\pm$ 2 grams	30 $\pm$ 2 grams
** 1st Postoperative Week	20 $\pm$ 9	39 $\pm$ 4
* 2nd Postoperative Week	24 $\pm$ 7	34 $\pm$ 7

TABLE I

Means ($\pm$SDs) of weight gained by rats with a unilateral microinjection of 6-OHDA into the MFB and by controls in the immediate preoperative week, first postoperative week and second postoperative week. First postoperative week means the 7-day period following the record taken 44hrs after surgery (see 3:2(ii)).

* $p < 0.01$

** $p < 0.001$

Mann-Whitney U test, one-tailed.

Records were not taken on the day immediately following surgery. However, the first postoperative records (taken 44hrs after surgery) showed that whereas 7 out of the 9 control ss had regained their preoperative highest recorded body weights, the experimental ss had not made a similar recovery except in the case of the animal with only an 86% loss of striatal DA on the lesioned side (Table II). The difference between the two groups in weight gained over the 44hr period between surgery and the first postoperative record is statistically significant ($p<0.001$, Mann-Whitney U test, one-tailed). On the other hand, there was not a significant difference between the two groups of ss in weight lost as a result of 24hr food deprivation or in weight recovery (=amount of weight gained) 24hrs after the restoration of food or in total weight gain recorded over these 48hrs taken together.

In Table III are shown the body weight changes in the food-deprivation and food-restoration periods; the table shows also the total weight gain displayed over these 48hrs taken together.

Food intake (that is, absolute amount in grams of food actually eaten) was not significantly different between the experimental and control groups prior to surgery (Mann-Whitney U test). Postoperatively, on the other hand, the experimental group ate significantly smaller quantities of food than the control group, during the first postoperative week ($p<0.001$, one-tailed test), during the second postoperative week ($p<0.001$, one-tailed test), during the 24hr of post-starvation feeding ($p<0.001$, one-tailed test), and during 1 week of recorded observation three months after surgery ($p<0.001$, one-tailed test). Statistical analysis of data was by the Mann-Whitney U test in all postoperative stages/

stages as in the preoperative stage of the investigation. The food intakes of the experimental and control groups, recorded in grams, over the various periods just referred to are presented in Table IV (see also Appendix B).

Experimental Group of ss (6-OHDA LESIONED)		Control Group of ss (Partially-lesioned and Unlesioned).	
Subjects	Wt Gain	Subjects	Wt Gain
A	-14.7 grams	A*	6.5 grams
B	-20.5	B*	6.4
C	-10	C*	0
D	- 1.3	D	2.6
E	- 6.6	E	0.7
F	-15.5	F	1.8
G	-14.5	G	-0.6
H	0.5	H	0.5
		I	-1.3
Mean $\pm$ SD	-10 $\pm$ 7	Mean $\pm$ SD	2 $\pm$ 3

TABLE II

Weight gained in 44hrs after surgery. The difference between the experimental and control groups is significant ($p<0.001$, Mann-Whitney U test, one-tailed). In the experimental group only Subject H displayed an increase in this period; in this regard it should be noted that whereas all the other experimental ss suffered more than a 95% depletion of striatal DA on the lesion side, this particular animal retained 14% of the DA content of its ipsilateral striatum (see Table VIII)

*Partially lesioned control ss.

Subject Groups	Subjects	Wt Lost during food Deprivation	Wt Gained 24hrs after food Restoration	Total Wt Gain (48hrs)
Experimental (6-OHDA-lesioned) Group	A	23.3 grams	24.1 grams	0.8 grams
	B	23.3	24.4	1.1
	C	23.6	24.0	0.4
	D	26.7	23.9	-2.8
	E	14.4	21.7	7.3
	F	27.5	19.8	-7.7
	G	24.8	20.3	-4.5
	H	24.0	17.9	-6.1
	Mean±SD	23±4	22±2	-1.4 ± 5
Control (partially lesioned and Unlesioned) Group	A*	29.0	26.2	-2.8
	B*	30.2	26.5	-3.7
	C*	25.5	25.1	-0.4
	D	21.0	18.7	-2.3
	E	24.0	20.9	-3.1
	F	25.8	20.8	-5.0
	G	25.2	20.5	-4.7
	H	25.1	24.5	-0.6
	I	30.3	24.9	-5.4
	Mean±SD	26±3	23±3	-3±2

TABLE III

Weight changes observed following food deprivation and 24hrs after food restoration. The differences between the experimental and control groups were not statistically significant (Mann-Whitney U test).

*Partially lesioned control ss.

Periods	Experimental Group of ss	Control Group of ss
Immediate Preoperative Week	150 ± 9 grams (N=8)	147 ± 10 grams (N=9)
■ 1st Postoperative Week	112 ± 25 (N=8)	161 ± 13 (N=9)
■ 2nd Postoperative Week	149 ± 16 (N=8)	195 ± 11 (N=9)
■ 23hrs of Feeding following a period of Food deprivation.	28 ± 3 (N=8)	35 ± 2 (N=9)
■ 14th Postoperative Week	172 ± 13 (N=5)	202 ± 19 (N=6)

TABLE IV

Means (±SDs) of food intake by rats with a unilateral 6-OHDA lesion of the nigrostriatal DA pathway and by controls.

■ $p<0.001$

Mann-Whitney U test, one-tailed.

For a detailed presentation of the data shown in this Table see Appendix A.

The spillage of food in the process of consumption did not show a significant difference between the experimental and control groups of ss preoperatively when compared statistically using the Mann-Whitney U test. A similar statistical comparison of postoperative food spillage habits, on the other hand, revealed that the experimental group spilled much more food in the course of feeding than the control group. Since the quantity of food spilled by an animal depends, in the final analysis, upon the quantity removed from the food-hopper for the purpose of feeding it was judged more meaningful to treat food-spillage in terms of the ratios of food spilled to food missing from the food-hopper than in terms of the absolute quantities of food spilled. Table V shows the mean ratios for the experimental and control groups in the 1wk preceding surgery, during the first postoperative week, during the second postoperative week, during the 24hrs of post-starvation feeding and during the 1wk of recorded observation which occurred three months after surgery. All the postoperative records showed a significant difference between the two groups of ss ($p<0.001$, Mann-Whitney U test, one-tailed).

The production of faeces was judged to be more meaningfully presented in terms of the ratio of faeces passed to food actually ingested than in terms of the absolute quantity (i.e. weight) of faeces passed, since the quantity of faeces produced is determined partly by food intake. It was assumed that the more food an animal ingests the greater the quantity of faeces it produces. This assumption is obviously true to a point. Moreover, in the author's experience there is a certain amount of consistency among normal rats of the same age in the relationship between quantity of faeces passed and quantity of food ingested over a period of three days or more.

Periods	Experimental Group of Ss	Control Group of Ss
Immediate Pre-operative Week	0.14 ± 0.01 (N=8)	0.14 ± 0.03 (N=9)
* 1st Postoperative Week	0.34 ± 0.1 (N=8)	0.16 ± 0.02 (N=9)
* 2nd Postoperative Week	0.33 ± 0.1 (N=8)	0.16 ± 0.02 (N=9)
* 24hrs of Feeding following a period of Food Deprivation	0.32 ± 0.11 (N=8)	0.15 ± 0.03 (N=9)
* 14th Postoperative Week	0.23 ± 0.04 (N=5)	0.15 ± 0.02 (N=6)

TABLE V

Means (±SDs) of ratios of food spilled to food bitten off in the process of feeding by the experimental (6-OHDA-lesioned) and control (partially lesioned and unlesioned) groups of ss.

*$p < 0.001$

Mann-Whitney U test, one-tailed.

Because the data relating to water intake were discarded owing to irregularities noticed in the recording procedure (see 3:3(i)) it is not possible to relate the production of faeces to water consumption.

The mean ratios of faeces passed to food ingested by the experimental and control groups of ss are shown in Table VI, as recorded for 1wk just before surgery, for the first postoperative observation week, for the second postoperative observation week and for the 14th postoperative week. There was not a significant difference between the two groups of ss in any of these periods of recorded observations (Mann-Whitney U test).

Periods	Experimental Group of Ss	Control Group of Ss
Immediate Preoperative Week	0.35 $\pm$ 0.04 (N=8)	0.35 $\pm$ 0.03 (N=9)
1st Postoperative Week	0.34 $\pm$ 0.04 (N=8)	0.36 $\pm$ 0.02 (N=9)
2nd Postoperative Week	0.34 $\pm$ 0.03 (N=8)	0.36 $\pm$ 0.03 (N=9)
14th Postoperative Week	0.37 $\pm$ 0.01 (N=5)	0.37 $\pm$ 0.02 (N=6)

TABLE VI

Means ($\pm$SDs) of ratios of faeces passed to food actually ingested by rats with a unilateral microinjection of 6-OHDA into the MFB and by controls. The differences between the experimental and control groups are not statistically significant (Mann-Whitney U test).

3:3(ii) ACQUISITION AND PERFORMANCE OF OPERANT BEHAVIOUR, LEVER PREFERENCE AND SPONTANEOUS ROTATION

ACQUISITION OF OPERANT BEHAVIOUR

The results appertaining to the acquisition of operant behaviour are presented in Table VII. Whereas the 6 control ss subjected to an operant behaviour training program in the Skinner box attained the criterion of learning in the first day of training (that is, within 90min of "semi-massed" practice), 2 of the 7 experimental ss subjected to an identical training program failed to reach criterion in three days (for details of the training procedure refer to 2:2). Of the 5 experimental ss reaching criterion only 1 did so in the first day of training; another appeared to have reached the criterion of learning by the end of the first day of training but failed to show any signs of learning when tested the following day, although it finally learned by the third day. The other three experimental ss reaching criterion did so in the third day of training. One of the ss failing to reach criterion during the three days of training seemed to have learned by the end of the first day of training but never showed signs of learning after that day.

PERFORMANCE OF OPERANT BEHAVIOUR:

All the 5 experimental ss which acquired lever pressing for food reward used virtually only the forepaw on the same side as the lesion when they pushed the lever; the control (unlesioned) ss, on the other hand, displayed a random pattern of forepaw use - 3ss pressing predominantly or exclusively with the forepaw on the same side as the injected MFB, and the other 3 ss using the contralateral forepaw

for/

for most or all of their lever-presses. The experimental ss made all their abortive lever-presses with the ipsilateral forepaw - the forepaw used for their entire effective (rewarded) lever-presses. Similarily the control group made most of their abortive presses with the same forepaw as that used predominantly for their effective presses except that one control s made 5 abortive presses with the forepaw less frequently employed for effective presses and only 1 abortive press with the dominant forepaw. Figures 7ā(i) and 7a(ii) depict the mean patterns of effective and abortive forepaw use displayed in the two groups of ss.

Rate of lever-pressing was significantly lower in the experimental (lesioned) group than in the control (unlesioned) group ($p<0.005$, Mann-Whitney U test, one-tailed test). The rates of lever-pressing displayed by the two groups are presented in Figure 7b in terms of number of effective presses executed in 20min of testing.

LEVER CHOICE:

Lever-preference was random in both the experimental and control groups. Thus, for example, 2 experimental ss showed a clear preference for the lever on the same side as the lesioned MFB and the other 3 experimental ss chose the contralateral lever for all or virtually all their effective presses. Figure 7c shows the mean patterns of lever-preference displayed in the experimental and control groups. Statistical treatment of the data (sign test) showed that there was not a significant difference in either group between the number of times they effectively depressed the ipsilateral lever and the number of times they effectively depressed the contralateral lever.

SPONTANEOUS ROTATION: /

SPONTANEOUS ROTATION:

The records regarding spontaneous rotation showed that 4 of the 5 experimental ss performed between 10 and 29 rotations, all towards the lesion side, in the 20min of testing; the 1 remaining experimental s, however, circled only six times, although all its rotations were ipsiversive as were those of the other experimental ss. The 6 control ss rotated between once and seven times during the 20min of testing and the direction of rotation was randomly distributed among the animals, and in three cases in the same animal as well. Figure 7d(i) depicts the mean directional preferences exhibited in the two groups of ss in spontaneous rotational behaviour. The mean total number of rotations performed in each group is shown in Figure 7d(ii); the difference between the two groups is statistically significant ($p<0.005$, Mann-Whitney U test, one-tailed).

Subject Groups	*Subjects Trained	Subjects Reaching Criterion	■Days Taken to Reach Criterion
	A	A	3
	B		
Experimental	C	C	1
	D	D	3
Group	E		
	F	F	3
	G	G	3
	D	D	1
	E	E	1
Control	F	F	1
	G	G	1
Group	H	H	1
	I	I	1

TABLE VII

Time taken by rats with a 12wk-old unilateral microinjection of 6-OHDA into the MFB and by controls to acquire a food-rewarded operant response.

* The ss are the same as those with an identical label in Tables II, III, and VIII.

■ A 60-min training session followed two hours later by a similar 30-min session constituted one day of training (see 2:2).

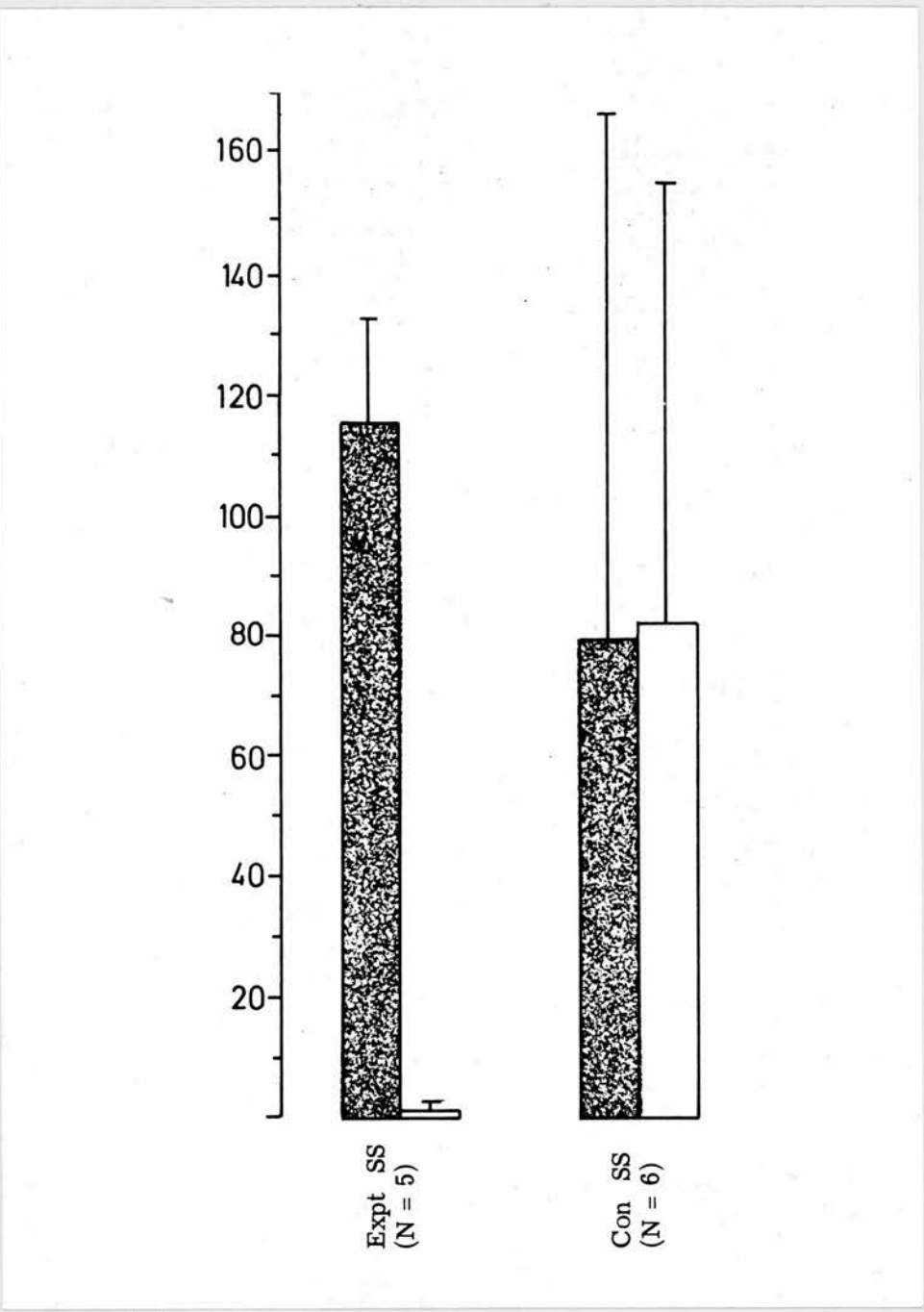


FIGURE 7a(i)

Mean patterns of effective (i.e. rewarded) forepaw use displayed in the 6-OHDA-lesioned and control groups of ss trained 12wks after surgery to lever-press for food reward. The columns represent the mean number of effective lever-presses executed in each group with the forepaw ipsilateral (stippled columns) or contralateral (open columns) to the operated hemisphere in a 20min operant behaviour session. Each bar represents one SD. The experimental group used only the ipsilateral forepaw; whereas the control group exhibited a random pattern of forepaw use. The difference in the control group is not statistically significant (Wilcoxon matched-pairs signed-ranks test).

Abbreviations: Expt. ss, experimental group of subjects; Con ss, control group of subjects.

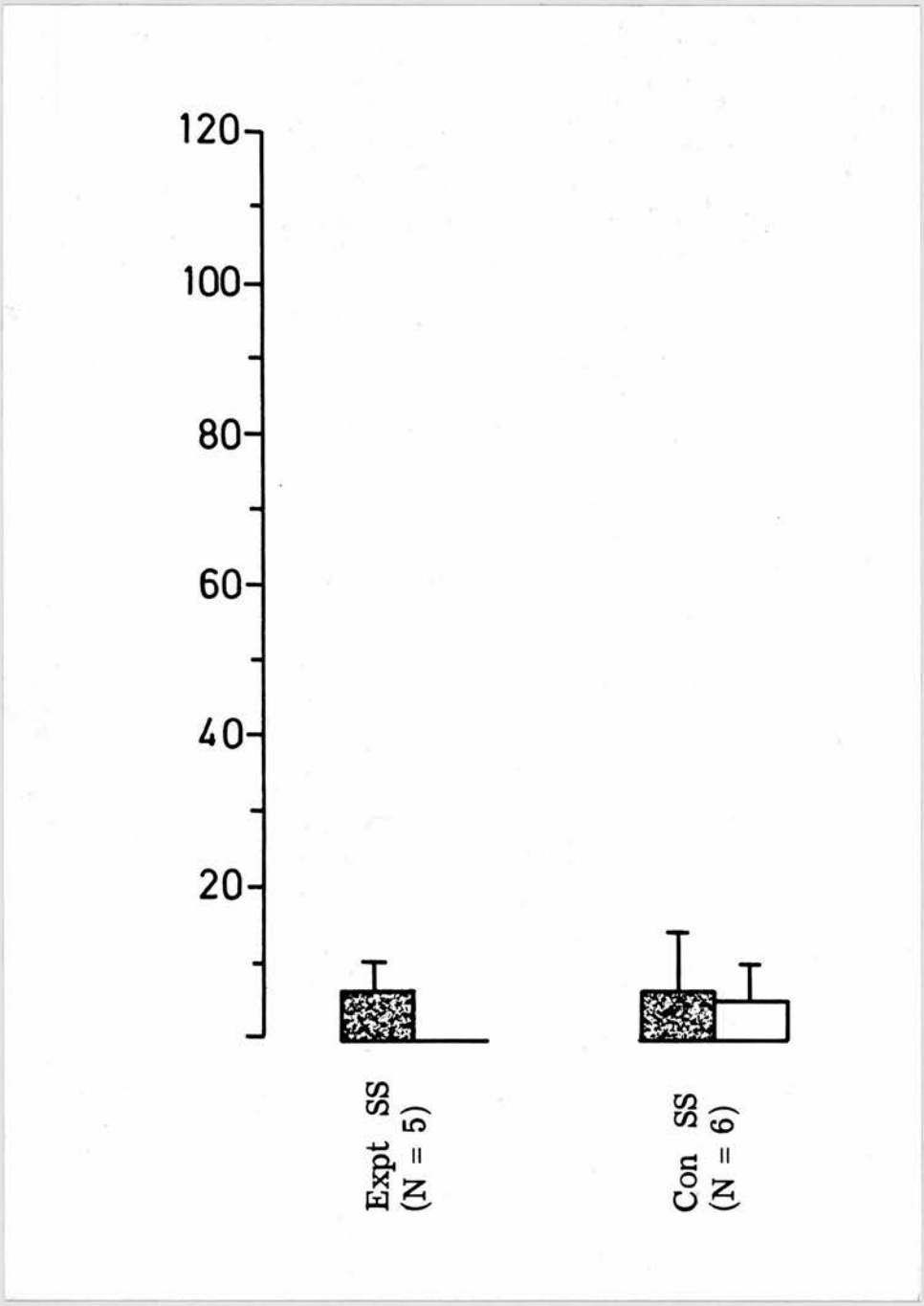


FIGURE 7a(ii)

Mean patterns of abortive (i.e. subthreshold) forepaw use in the 6-OHDA-lesioned and control groups of ss trained 12 wks after surgery to lever-press for food reward. The columns represent the mean number of abortive lever-presses made with the forepaw ipsilateral (stippled columns) or contralateral (open columns) to the operated side of the brain in a 20min operant behaviour session. Each bar represents one SD. The experimental group made all their abortive presses with the ipsilateral forepaw, whereas the control group displayed a random pattern of forepaw use and there was not a significant difference in the control group between the ipsilateral and contralateral forepaws in the performance of abortive presses(Wilcoxon matched-pairs signed-ranks test).
Abbreviations: Expt. ss, experimental group of subjects; Con ss, control group of subjects.

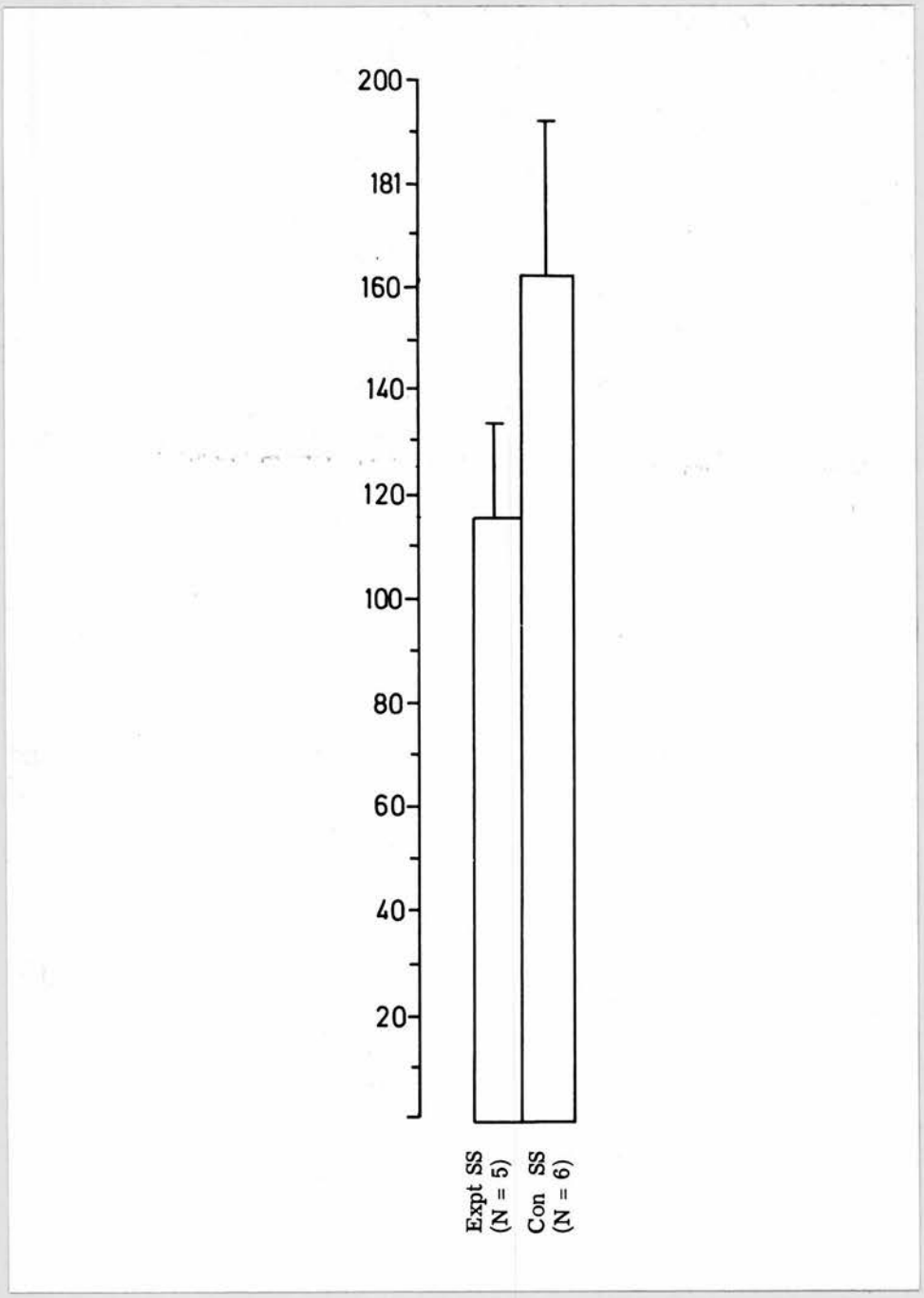


FIGURE 7b:

Mean number of effective lever-presses executed in a 20min session by 6-OHDA-lesioned and control groups of ss trained 12wks after surgery to lever-press for food reward on a continuous reinforcement schedule. Each bar represents one SD. The difference between the two groups is statistically significant ($p<0.005$, Mann-Whitney U test, one-tailed). Abbreviations: Expt. ss, experimental group of subjects; Con ss, control group of subjects.

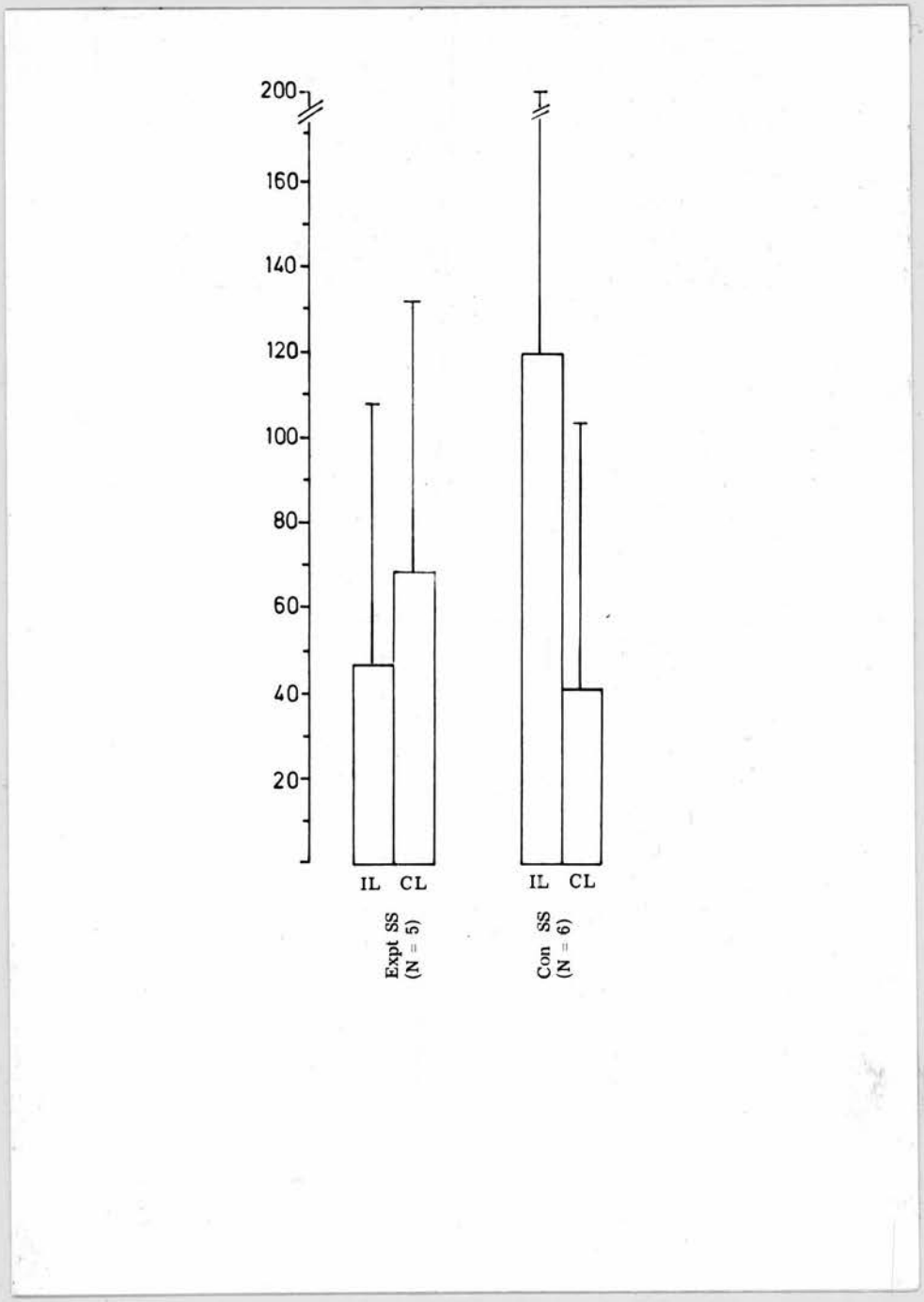


FIGURE 7c:

Mean patterns of lever choice displayed in a 20min session by 6-OHDA-lesioned and control groups of ss trained 12wks after surgery to lever-press for food reward in a two-lever Skinner box. Lever choice was random in each group and the difference is not statistically significant in either group (sign test).

Abbreviations: IL, ipsilateral lever; CL, contralateral lever; Expt ss, experimental subjects; Con ss, control subjects.

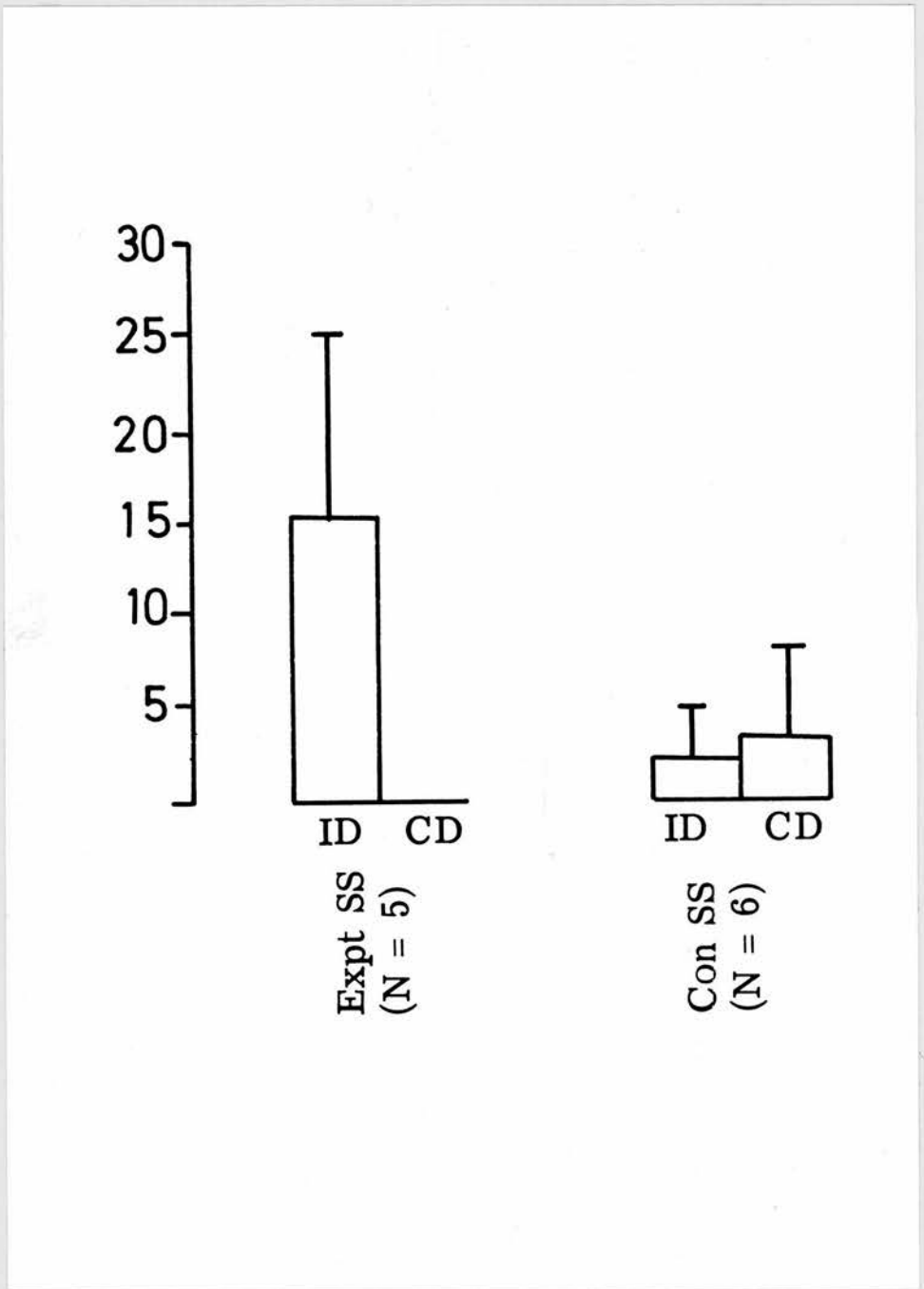


FIGURE 7d(i):

Mean number of rotations performed in each direction in a 20min operant behaviour session by 6-OHDA-lesioned and control groups of ss trained 12wks after surgery to lever-press for food reward. Whereas all the experimental ss rotated only toward the lesion side, direction of turning exhibited by the control group was random; the difference between the ipsiversive and contraversive directions of circling was not statistically significant in the control group (Wilcoxon matched-pairs signed-ranks test).

Abbreviations: ID, ipsiversive direction; CD, contraversive direction, Expt ss, experimental subjects; Con ss, control subjects.

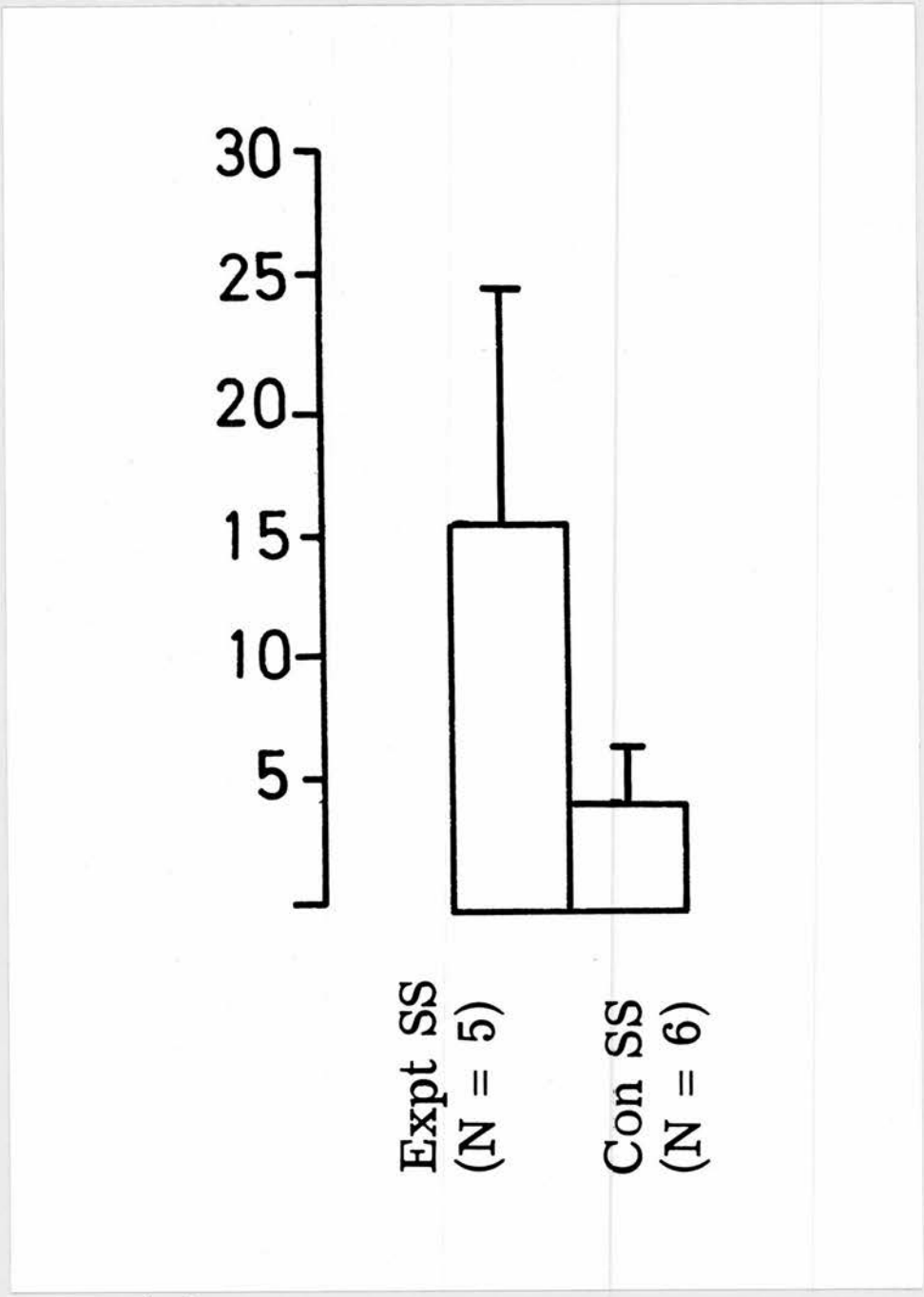


FIGURE 7d(ii):

Mean total rotations performed in a 20min operant behaviour session by 6-OHDA-lesioned and control groups of ss trained 12wks after surgery to lever-press for food reward. The difference is statistically significant ($p<0.005$, Mann-Whitney U test, one-tailed).

Abbreviations: Expt SS, experimental group of subjects; Con SS, control group of subjects.

3:3(iii) CATECHOLAMINE ASSAY RESULTS:

The DA and NE assay results are presented in Table VIII. Of the 11 ss given a unilateral microinjection of 6-OHDA aimed at the MFB, 7 sustained a DA depletion of 95% or more in the striatum on the lesion side and 1 other s sustained an 86% loss; the drop in ipsilateral striatal DA content suffered by the remaining 3 ss ranged from 30% to 64%. As the table shows 6-OHDA microinjection also caused reductions in the NE content of the denervated striatum and in the DA content of the corresponding limbic forebrain region, although limbic forebrain NE was unaffected in five of the eight ss sustaining a substantial loss of DA in the ipsilateral striatum. The 6 control ss did not show a consistent drop of any degree at all in the DA or NE content of the ipsilateral striatum or limbic forebrain.

There was no significant correlation between the intensity of lesion-induced alterations in ingestive behaviour and body weight regulation and the severity of damage to any one neurochemical system in any of the brain regions sampled (Kendall's tau). However, the rat sustaining the least neurochemical depletions (striatal DA, 86%; limbic forebrain DA, 95%; striatal NE, 65%; limbic forebrain NE, 0%) displayed little or no deficit in food intake and body weight.

3:3(iv) RETROGRADE DEGENERATION OF ZONA COMPACTA CELLS FOLLOWING 6-OHDA MICROINJECTION INTO THE MFB.

Histological examination of the substantia nigra of selected ss (3:2(vi)), which had been used for both the feeding and operant behaviour experiments, revealed that the zona compacta of the substantia nigra on the lesion side of the experimental ss had disappeared; the corresponding structure on the opposite side was intact. As was expected the control ss did not show a similar cell loss on the injected

side. The photographs constituting Figure 8 show the two sides of the brain in a typical experimental s; it can be seen that the normally prominent zona compacta column of cells is missing from the picture in Plate A (the lesion side).

Subject Groups	Subjects	DOPAMINE Striatum	DOPAMINE Limbic Forebrain	NOREPINEPHRINE Striatum	NOREPINEPHRINE Limbic Forebrain
Experimental (6-OHDA-Lesioned) Group	A	100%	96%	93%	0%
	B	100	100	95	0
	C	100	100	86	75
	D	100	97	88	42
	E	100	96	91	0
	F	100	99	97	82
	G	100	100	99	0
	H	86	95	65	0
Control (partially lesioned + unlesioned) Group	*A	64	14	54	0
	*B	31	10	20	6
	*C	30	11	22	4
	D	18	0	0	1
	E	0	6	8	0
	F	9	3	20	26
	G	3	28	0	31
	H	0	0	27	0
	I	9	14	0	33

TABLE VIII

Percent catecholamine loss in the injected hemisphere of 6-OHDA-lesioned and control rats used in the experiments reported in Chapter 3.

*Partially lesioned control ss; these ss and subject H of the experimental group were not used in the operant learning experiment (see 3:2(iii)).

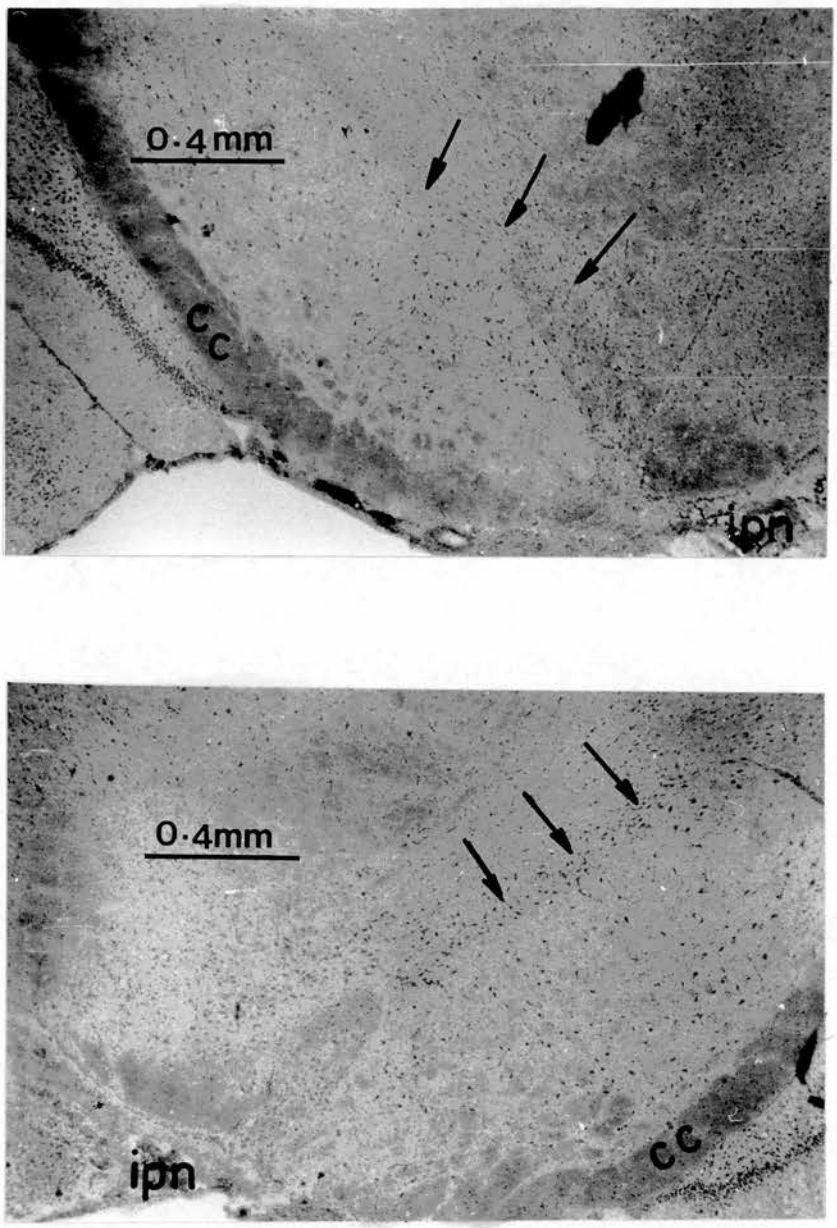


FIGURE 8:

Photomicrographs showing the substantia nigra in each hemisphere of the brain of a rat given a unilateral microinjection of 6-OHDA into the MFB. Plate A displays the substantia nigra of the lesion side. It can be seen that the normally prominent zona compacta column of cells (see arrows in Plate B) is missing from Plate A.

Abbreviations: CC, Crus cerebri; ipn, interpeduncular nucleus.

3:4 DISCUSSION

3:4(i) BODY WEIGHT AND FEEDING BEHAVIOUR

The observation that rats sustaining an extensive unilateral lesion of the nigrostriatal DA system as a result of 6-OHDA microinjection into the MFB lost weight substantially and remained underweight for a long time (Figure 6) confirms the finding of Baez et al. (1977). Also the finding that such animals eat significantly less food than injected controls supports the suggestion by these authors that the observed effect of lesion on body weight was due to reduced food intake.

Every one of the lesioned animals spilled more food than any of the controls per unit amount bitten off in the process of feeding (Table V). It is tempting, therefore, to conclude that the observed reduction in actual food intake was due, at least in part, to sensorimotor dysfunction reflected in increased food spillage.

Doubt regarding the existence of sensorimotor impairment in lesioned animals tends to recede when one considers the fact that all the lesioned ss acquiring lever pressing for food reward in a Skinner box used exclusively the ipsilateral forepaw, unlike controls, which, as a group, displayed random forepaw use. The apparent incapacitation of the contralateral forepaw following a unilateral nigrostriatal damage would appear to imply that the nigrostriatal pathway is part of a lateralized system controlling sensorimotor function. It may be, therefore, that the nigrostriatal system, like the pallidum (Levine and Schwartzbaum, 1973; Levine et al., 1971), must be functional if an animal is to use effectively the musculature of its limbs and mouth, and possibly certain other organs as well. If this view is correct the acute aphagia and adipsia/

adipsia observed in animals with bilateral nigrostriated damage (Fibiger, Zis and McGeer, 1973a; 1973b; Marshall and Teitelbaum, 1973; Marshall et al., 1974; Stricker and Zigmond, 1974; Ungerstedt, 1971a) are probably due, at least in part, to sensorimotor dysfunction.

The fact that some of the unilaterally lesioned animals of the present experiment frequently bit off more food than controls in the process of feeding (Appendix B) may represent an effort to make up for the huge amounts lost through spillage. It might be argued, therefore, that the reduction of food intake following lesion was not associated with any impairment of motivation but was ultimately due to a disruption of sensorimotor functioning. However, it seems important to note that following 24hrs of food deprivation all ss, lesioned and unlesioned alike, ingested more food in one day than they ever did in a comparable period under conditions of unlimited food availability. Although unlesioned animals ate significantly more food than lesioned ones following food deprivation as well as under ad lib. conditions, it is interesting that under suitable conditions the lesioned ss exceeded their usual level of food intake in spite of their sensorimotor disability. In the light of this observation it seems reasonable to conclude that restriction of food intake by the lesioned animals was not imposed by sensorimotor dysfunction alone.

There are several factors which have been identified as important in determining the amount of food ingested by an animal. These include temperature (Brobeck, 1948), blood glucose (Mayer, 1953; Mayer and Arees, 1968), total fat content of the animal (Kennedy, 1953; 1966), and endocrine factors (for a review, see Bray, 1974). Using such factors, Russek (1976) has proposed a mathematical model whereby it should be possible, given their precise values, to predict food intake. In his model Russek

ascribes to the hepatic glucoreceptors the function of modulating the rate of food intake. In order to account for long-term stability of body weight, he invokes the concept of a set-point for body weight. This latter suggestion has been challenged by Garrow (1974, 1978) in two different editions of his book on obesity in man. Garrow (1978) has noted that "the short-term control of food intake in man is so erratic that it is difficult to detect any sort of regulation from day to day, still less any set point". To support his argument Garrow quotes the experiments of Walike, Jordan and Stellar (1969), Wooley, Wooley and Dunham (1972), and Pudel and Oetting (1977) which demonstrated that both fat and lean persons are fallible in assessing their own energy intake and adjusting correctly the size of the following meal. He also refers to the finding by Ashworth, Creedy, Hunt, Mahon and Newland (1962) that an intragastric load of 2000K cal every night for 36 nights did not affect the voluntary daily food intake of normal volunteers. Garrow concedes that "long-term control of intake must be quite good since body weight in most people is fairly stable", but points out that the weight of an adult person may still vary by several kilograms upward and/or downward over a long-term observation period.

The set-point theory has also come under attack from other authors. Notable among these are Payne and Dugdale (1977), who pointing out that "body-weight is not constant in a normal adult" have proposed a control system which does not employ a set point reference system. According to their model, the mechanisms working to keep the weights of human adults fairly stable include hunger and satiety, the relative constancy of habits and customs of behaviour, and the existence of cognitive thresholds combined with a negative feedback system.

The set point theory is still widely defended, however, particularly with regard to body weight regulation in animals. B.G. Hoebel and P. Teitelbaum (Teitelbaum, 1961) demonstrated many years ago (a) that if a rat was made obese by inducing overeating through daily injections of protamine zinc insulin it would not overeat to an extent that would increase its weight much further after lesions of the ventromedial hypothalamus, as would uninjected, preoperatively non-obese rats, and (b) that if a normal rat was induced to overeat by insulin injections and to become obese as a result, it would, after the injections were discontinued, eat much less until its weight returned to a normal level. On the basis of these findings Teitelbaum (1961) proposed that animals eat to achieve a target or set point in body weight. Several more recent animal experiments have yielded results which appear to support this hypothesis. Boyle, Storlien and Keesey (1978) have reported increased efficiency in food utilisation (as determined in terms of amount of weight gained per unit amount of food ingested) following weight loss. In another report Keesey, Boyle and Storlien (1978) have shown that although rats with LH lesions do, like normal rats, adapt to weight loss by increasing their efficiency in food utilisation, such adjustments occur around a reduced level of maintained body weight. Another interesting study is one by Kolb, Whishaw and Schalbert (1977) in which they found that rats sustaining discrete bilateral lesions in the orbital frontal neocortex assumed a chronic post-operative body weight level 25% lower than control ss, irrespective of whether they had been fattened or dieted or allowed free and voluntary access to normal laboratory food prior to surgery. The authors interpreted this observation as indicative of a "change in body weight set point".

The set point theory might account for the fact that the 6-OHDA-lesioned animals in the present study ate more food than usual following

food deprivation - an observation that cannot be explained adequately in terms of sensorimotor or motivational impairment. It would appear that all the animals used in the experiment ate more following food-deprivation in order to make up for something lost and that under conditions of ad lib. food supply they did not need to eat so much. This interpretation does not, of course, exclude the possibility that the depression of food intake and body weight observed after a 6-OHDA lesion in the experimental ss might have been due to regulatory changes affecting such intake-related factors as blood glucose levels, body fat levels and endocrine functions. Unfortunately, the present study did not determine whether or not these changes occurred as a result of 6-OHD[A] lesions. What is here suggested is that a reduced set point in body weight might be an important factor leading to the lower level of food intake observed in the 6-OHDA-lesioned rats.

The finding that lesioned animals pass roughly the same quantity of faeces as controls per unit amount of food ingested (Table VI) shows that the "utilization" of food at the level of the alimentary tract is not impaired by a unilateral nigrostriatal lesion. It does not, though, exclude the possibility that such a lesion might be accompanied by a disruption of the assimilation stage of the food-utilization process, This, in fact, is a possibility worth investigating.

It would be interesting, furthermore, to know the duration and frequency of meal times displayed by lesioned vis-a-vis control animals, as there is the possibility that differences between the two groups in food intake might in effect be due to differences in the duration and frequency of meal times. Unfortunately, it was not possible in the present study to investigate meaningfully the duration and frequency of meal times, owing to restrictions of access to animals outside the hours/

hours of the day when the animal house was open.

Judging strictly from the results of the study, therefore, one is compelled to conclude as follows:

(a) animals with a unilateral nigrostriatal lesion of the kind used display sensorimotor dysfunction;

(b) they also suffer a deficit in food intake and body weight;

(c) the reduced food intake encountered in such animals might be due, in part, to a lowering of their body weight targets.

3:4(ii) LEARNING AND SENSORIMOTOR PERFORMANCE

There appears to have been an impairment of the capacity to learn operant responses following unilateral nigrostriatal damage since the lesioned group generally took longer than the unlesioned (control) group to reach criterion and since in fact two of the lesioned ss failed to learn in three days of training (3:3(ii)). This observation appears to support the finding by Ranje and Ungerstedt (1977) that bilateral nigrostriatal damage impairs the capacity to acquire certain kinds of learning. Furthermore, the fact that two lesioned ss appeared to have reached criterion and then showed no signs of learning when tested the following day may be significant for the viewpoint that learning capacity had been basically disturbed. It seems that the disruptive effect of lesion on the learning capacity of these ss was primarily on the consolidation phase of the learning process, since the animals displayed learning on the first day of training and lost it after 24hrs of non-practice.

Such/

Such a viewpoint is in opposition, though, to the proposal by several other investigators that the failure by lesioned animals to display acquisition of a conditioned avoidance response was due to inability to initiate voluntary movements (Price and Fibiger, 1975; Smith, Levin, and Ervin, 1975). In this regard the tendency of lesioned animals in the present study to rotate compulsively would appear to be responsible for the initial delay in learning exhibited by the lesioned group. The forced rotation may have lowered the chances of making the prerequisite association between lever pressing and the availability of food at the food-tray, in which case the delaying effect of lesion on acquisition may not justifiably be explained entirely in terms of a basic disruption of the capacity to learn.

The effect of unilateral nigrostriatal lesion on the performance of operant behaviour was two-fold. Firstly, all the lesioned animals pushed the lever with only the forepaw on the same side as the lesioned nigrostriatal system, whereas only three out of six control ss used predominantly the forepaw ipsilateral to the operated hemisphere. Secondly, the lesioned group executed significantly fewer effective presses than the controls in the 20min of recorded observation. The exclusive use of the ipsilateral forepaw by the lesioned ss suggests that the nigrostriatal pathway is part of a lateralised system for sensorimotor control of the forelimbs, and appears to support the finding by Ljungberg and Ungerstedt (1976), and Marshall, Richardson and Teitelbaum (1974), that unilateral nigrostriatal damage causes sensorimotor impairments evident on the side of the body contralateral to the lesioned hemisphere. The low rate of effective lever pressing displayed by/

by the lesioned group, as compared to controls, in the present study is reminiscent of akinesia such as has been reported following bilateral damage (Olmans and Harvey, 1972; Ungerstedt, 1971a; Zigmond and Striker, 1972).

The apparent rate-depressing effect of unilateral nigrostriatal damage seems, on its face value, to put a question-mark on the interpretation given above with regard to reduced food intake by lesioned animals (3:4(i)) since both the low rate of lever pressing and the reduced food intake might have been caused by a kind of hypokinesia. In other words, reduced food consumption by the lesioned animals might not be due to the adoption of new (reduced) body weight targets as has been suggested. However, the fact that some lesioned animals actually bit off more food than controls in the feeding process (see Appendix B) argues somewhat against the hypokinesia interpretation, as biting action obviously involves energy mobilization. Moreover, the fact that the lesioned animals ate more food than usual at the end of a period of food-deprivation suggests that these animals fed partly to meet a homeostatic target of some kind, which is probably reflected in the body weight.

The likely effective cause of the apparent depression of lever-pressing rate in the unilaterally lesioned animals seems to be furnished by the frequent compulsive circling by these ss (Figure 7d(ii)). Circling takes time and number of lever presses obviously depends, in a sense, upon the amount of time available; besides, forced rotation in the operant behaviour situation may have produced an unknown array of emotional effects in the animal, and this may have led to energy dissipation and other disruptive consequences.

3:4(iii) SPONTANEOUS ROTATION AND SPATIAL PREFERENCE.

Two forms of spatial behaviour were observable in the Skinner box situation of the present study, as follows: spontaneous rotation and lever preference.

As we have seen (Figure 7d(i)), the group of ss with a unilateral nigrostriatal lesion rotated exclusively towards the lesion side during the 20-min observation period in the operant behaviour enclosure, whereas the control group displayed no consistent directional preference in their circling behaviour. This observation is in agreement with the reports of previous investigators that unilateral nigrostriatal damage leads to ipsiversive rotation (Anden et al., 1966; Christie and Crow, 1971; Ungerstedt, 1971e). Concerning lever choice, on the other hand, there was not a consistent preference in either group of ss for the lever ipsilateral or contralateral to the operated side of the brain. In other words, lever preference was apparently not determined by asymmetry between the two nigrostriatal systems of the animal. This observation is contradictory to the report by Glick and Jerussi (1974) that intact animals working for food reward in a two-lever operant behaviour situation tended to show preference for the lever on the same side as the striatum with the lower DA content. It is conceivable, however, that the discrepancy between the results of the present experiment and their's is due to a difference between the designs of the operant behaviour boxes used in the two experiments, although, unfortunately, a full description of their box is not available to the present author. The results of the present experiment regarding spatial behaviour show, in any case, that whereas in rats with unilateral nigrostriatal damage the direction of spontaneous rotation is determined by asymmetry between/

between the nigrostriatal systems in the two hemispheres, lever choice by such animals in a two-lever Skinner box of the design used in the study (see Figure 3) is not similarly determined.

3:4(iv) NEUROCHEMICAL EFFECTS OF 6-HYDROXYDOPAMINE MICROINJECTION INTO THE MEDIAL FOREBRAIN BUNDLE

From Table VIII it can be seen that the microinjection of 6-OHDA into the MFB led to a huge drop in the DA content of the striatum on the injected side. However, there were also consistent depletions of striatal NE and limbic forebrain DA. It is, therefore, not possible to conclude, on the strength of the results of the present study, that any behavioural effects attributable to the lesion procedure were due exclusively, or even in part, to the disruption of the nigrostriatal DA system. Nigrostriatal dopaminergic involvement is, though, more than a possibility, since the most pronounced neurochemical effect of the lesion is seen in the striatal DA level. Furthermore, the nigrostriatal DA pathway is intimately associated with the extrapyramidal system (Bedard et al., 1969), a network importantly involved in motor control (Poirier, 1976). However, further work is required to clarify the degree of importance of the role played by the nigrostriatal DA system in the behavioural functions disrupted by 6-OHDA microinjection into the MFB and to define the mechanisms of such a role. The studies reported in subsequent chapters of this thesis were designed for the most part to achieve these objectives.

CHAPTER 4

NIGROSTRIATAL DOPAMINERGIC CONTROL OF OPERANT BEHAVIOUR, SPATIAL BEHAVIOUR AND LEARNING

4:1 INTRODUCTION

4:1(i) THE NIGROSTRIATAL DOPAMINE SYSTEM AND SENSORIMOTOR FUNCTION

Impairments of sensorimotor function are known to be associated with electrolytic lesions of the LH (Marshall and Teitelbaum, 1974; Marshall, Turner and Teitelbaum, 1971). Also in rats rendered aphagia by bilateral LH lesions the initial recovery of eating corresponded with recovery of the capacity to orient to sensory stimuli (Marshall and Teitelbaum, 1974). It has, therefore, been concluded that sensorimotor deficits are a major cause of the aphagia and adipsia symptoms of the so-called LH syndrome (Marshall and Teitelbaum, 1974).

However, Levine and Schwarzbaum (1973) failed to obtain any effect on forepaw use following a unilateral LH lesion. These authors explained this rather surprising finding in terms of the relatively small reduction in striatal DA content known to have been associated with some aphagia-producing LH lesions (Oltmans and Harvey, 1972; Zigmond and Stricker, 1973).

On the other hand, a disruption of the sensorimotor control of the contralateral forepaw has been reported following a unilateral lesion of the pallidum (Levine and Schwartzbaum, 1973; Levine, et al., 1971) or of the entopeduncular nucleus (Levine and Schwartzbaum, 1973). Lesions of these areas interrupt the ascending nigrostriatal DA pathway (Moore, Bhatnagar and Heller, 1971; Ungerstedt, 1971d) and cause a reduction of striatal DA (Anden, Dahlstrom, Fuxe, Larsson, Olson and Ungerstedt, 1966).

In view of these and other related findings there is little wonder that the nigrostriatal pathway is widely assumed to be part of a lateralised system controlling the sensorimotor components of behaviour. This notion is the more probable if one takes into consideration the fact that this pathway is structurally related to the extrapyramidal system (Bedard, et al., 1969).

It may be recalled from the experiment presented in Chapter 3 of this thesis that rats sustaining a unilateral 6-OHDA-induced lesion of the nigrostriatal system spilled more food than controls in the process of feeding, and used only the ipsilateral forepaw to push the lever for food reward in a Skinner box. The studies reported in the present chapter were designed partly to provide a more rigorous verification of the sensorimotor role of the nigrostriatal DA system in terms of its influence on forelimb use.

4:1(ii) THE NIGROSTRIATAL DOPAMINE SYSTEM AND SPACE-RELATED BEHAVIOUR

The nigrostriatal DA system has been implicated in rotational behaviour in a variety of studies (for a review of such studies see 3:1(iv)). It may be recalled, furthermore (Chapter 3) that rats with a 12-week-old unilateral 6-OHDA lesion of the nigrostriatal system displayed a higher rate of spontaneous rotation than controls during an operant behaviour session in the Skinner box, and rotated exclusively toward the lesion side. The experiments in the present chapter which were set in the Skinner box were designed partly to verify this observation and relate it to forepaw use and to the form of spatial behaviour that may be reflected in lever choice in a two-lever operant behaviour situation.

The nigrostriatal DA system has also been reported to play an important role in side preference in a T-maze. Thus unilateral electrical stimulation of the caudate nucleus evokes contralateral side-preference (Zimmerberg and Glick, 1975), whereas a unilateral caudate lesion produces ipsiversive side preference (Rothman and Glick, 1976). Moreover, a correlation between rats' side preference in a T-maze and their direction of circling following D-amphetamine administration has been reported (Zimmerberg, Glick and Jerussi, 1974). It has, therefore, been proposed that side preference in a T-maze is determined by the relative dominance of one or the other nigrostriatal DA system of the brain (Zimmerberg, 1975; Zimmerberg et al, 1974).

One of the experiments reported in the present Chapter (4:2(B)) was designed primarily to test the hypothesis that rats trained to run a T-maze for food and then given a discrete (6-OHDA-induced) nigrostriatal lesion in the hemisphere opposite to the preoperatively preferred side of the maze will exhibit a reversal of side preferences when tested postoperatively.

4:1(iii) THE NIGROSTRIATAL DOPAMINE SYSTEM AND LEARNING

The nigrostriatal DA system has been found by several authors to be involved in the acquisition and performance of learned behaviour (for a review see 3:1(v)). A very interesting study in this regard is that of Ranje and Ungerstedt (1977) in which rats with bilateral nigrostriatal damage failed to acquire a discrimination task even under conditions that enabled them to overcome their lesion-induced akinesia. This finding is especially interesting because it suggests that nigrostriatal damage disrupts the capacity to learn - a suggestion that contradicts/

contradicts the proposal by some authors that the apparent inability of 6-OHDA-lesioned animals to acquire a conditioned avoidance response reflects lesion-induced akinesia (Price and Fibiger, 1975; Smith et al., 1975) rather than an impairment of learning capacity per se.

In Chapter 3 of this thesis it was reported that rats subjected to an operant behaviour training regime 12 weeks after a unilateral 6-OHDA lesion of the nigrostriatal system had displayed greater difficulty than controls in learning. This finding, like that by Ranje and Ungerstedt (1977), appears to implicate the nigrostriatal DA system directly in learning. Part of the work reported in the present chapter was aimed at verifying the previous finding, using a different set of rats that had a more recent unilateral lesion.

4:1(iv) SUMMARY OF THE REST OF THE CHAPTER

This Chapter presents three experiments. The first of these (see 4:2(A)(i); 4:2(A)(ii); 4:2(A)(iii); 4:2(A)(iv); 4:3(A)(i); 4:3(A)(ii)) investigated the effects of a unilateral nigrostrial lesion on the sensorimotor control of the forelimbs, rate of lever pressing in a food-rewarded operant-behaviour situation, lever preference in a two-lever Skinner box and rotational behaviour. In this experiment setsof experimental and control ss were observed in terms of these variables before and after surgery. In the second experiment (see 4:2(B)(i); 4:2(B)(ii); 4:2(B)(iii); 4:2(B)(iv); 4:3(B)(i); 4:3(B)(ii)), T-maze behaviour was investigated with particular reference to side preference, goal preference and running speed. In this experiment also the ss were observed both before and after surgery. The third experiment (see 4:2(C)(i); 4:2(C)(ii); 4:3(C)(i); 4:3(C)(ii)) investigated the acquisition/

acquisition and performance of food-rewarded lever pressing by the ss used in the second experiment. Also observed in these ss were their rotational behaviour and their patterns of lever choice in a two-lever Skinner box.

EXPERIMENT I: NIGROSTRIATAL DOPAMINERGIC CONTROL OF OPERANT AND SPACE-RELATED BEHAVIOUR IN THE SKINNER BOX

4:2(A) MATERIALS AND METHODS

4:2(A)(i) SUBJECTS

The ss were 29 male Wistar albino rats weighing between 175g and 200g at the time of surgery. Throughout the study the animals were kept two per cage in RC1 cages of the North Kent Plastic Cages Ltd., in a reverse daylight room, as previously described (2:1). The ss had unlimited access to food and water except that (a) they were deprived of food for 24hrs or 48hrs as judged appropriate (2:2) at specific points in the study (4:2(A)(ii)) to prepare them for operant behaviour sessions, (b) they had no water during operant behaviour sessions, and (c) during periods of data-gathering operant behaviour sessions they received just enough daily food supply to keep them at about 80% of their expected body weights.

4:2(A)(ii) SENSORIMOTOR FUNCTION AND SPATIAL BEHAVIOUR IN THE SKINNER BOX

At the end of an environmental orientation period (see 2:1) the ss were deprived of food for 48hrs, although water remained available. Following food-deprivation the ss were trained to press a lever for food in a two-lever Skinner box according to a procedure already described (2:2).

The/

The ss were free to operate either lever, and an s received, for every push that depressed the lever, a single 45mg food pellet (Campden Instruments, London).

When an s reached learning criterion (2:2) and confirmed 24hrs later on its acquisition of the operant response (2:2) it was passed as trained and ready for data-gathering sessions. Over the next two days the ss were given two recorded (i.e. data-gathering) sessions of 25min each - one session per day. Then the animals underwent surgery according to a procedure previously described (2:5).

Following surgery the ss were left undisturbed for seven days before postoperative testing was started. It was hoped that in the seven days immediately following surgery not only would nerve degeneration, where applicable (see 2:2; 4:2(A)(ii)), be completed (Anden et al, 1972; Hokfelt and Ungerstedt, 1969), but also all ss would have got over the acute effects of surgery. At the end of the 1 week recovery period the ss were deprived of food for 24hrs in preparation for the early postoperative data-gathering sessions; two such sessions lasting 25min each were given, one session per day, on two consecutive days. Thereafter all behavioural studies were suspended until 8 weeks elapsed from the day of surgery, hopefully to allow complete degeneration of the nigrostriatal DA pathway and any associated compensatory events to occur. Then after another 24hr period of preparatory food deprivation the ss were given two "retest" (late postoperative) sessions on two consecutive days - each session lasting 25min as usual.

Following 24hrs of food deprivation the weight of a rat is reduced to about 92% of its pre-deprivation level (see Table III and Figure 6). In the present study it was observed that at the end of 48hrs of food deprivation/

deprivation in the preoperative phase the ss measured approximately 85% of their pre-deprivation weights. Furthermore, all the ss in this experiment maintained, throughout the two-day periods of data-gathering (recorded) observation, their weights as at the beginning of these periods, receiving in the meantime only such food as they could obtain during the operant behaviour sessions. Therefore, it was not deemed necessary to feed the animal further after an operant behaviour session.

The variables observed and recorded in the data-gathering sessions were: number of effective lever presses executed with each forepaw; number of abortive presses made with each forepaw; total number of effective presses; number of times each lever was effectively operated and number of rotations in each direction (left/right). Recording of quantitative observations was carried out with the combined help of a manually operated multiple channel counting device and a set of electromagnetic counters as outlined in the chapter on techniques (see 2:2).

4:2(A)(iii) SURGERY

The animals were anaesthetized with a saturated fluothane/air mixture and maintained under anaesthesia by having a 1% fluothane/air mixture circulated through a mask fitted over the nose for the duration of the surgical operation. A general account of the surgical procedure has already been given (2:5).

Twenty-three rats originally intended to serve as experimental ss were given a unilateral microinjection of 6-OHDA (8ug in 4ul of isotonic saline containing L-ascorbic acid at the concentration of 0.1 mg/ml) into the MFB. Of this number 13 ss were injected on the side opposite to the forepaw/

forepaw used for most of the preoperative lever presses, whereas the other 10 ss were injected on the same side as the preoperative forepaw preference. Six primary control ss were injected with the bare vehicle (4ul of isotonic saline containing 0.1 mg/ml L-ascorbic acid) on the side opposite to the preoperatively preferred forepaw; they did not receive 6-OHDA with it. Any 6-OHDA-treated ss in which the MFB target was missed were to serve as secondary control ss.

At the end of each injection 4min were allowed to expire before the cannula was removed, the hole made in the skull in the process of surgery covered and the wound given an antiseptic spray and sutured.

4:2(A)(iv) DISSECTION AND VERIFICATION OF LESION

All the ss in this experiment were sacrificed between three and six weeks after the late postoperative data-gathering sessions in the Skinner box (4:2(A)(ii)). The animals were killed by being stunned and then decapitated. Left and right striatal samples and left and right limbic forebrain samples were dissected out according to a procedure described earlier (2:9). The samples were used for the radioenzynatic determination of DA and NE contents of the brain regions sampled. Assay of these catecholamines was by the method of Coyle and Henry (1973) and Palkovitz et al (1973), a full account of which has been presented in Chapter 2 (2:12). The striatal levels of DA in the two hemispheres would show the extent of nigrostriatal dopaminergic damage while the striatal NE levels and the limbic forebrain levels of DA and NE would indicate any unintended damage to catecholamine systems supplying the forebrain.

4:3(A)/

4:3(A) RESULTS

4:3(A)(i) BEHAVIOURAL STUDIES

All the 9 ss with 6-OHDA destruction of the nigrostriatal DA system contralateral to the preoperatively preferred forepaw stopped pressing the lever mainly with that paw and tended to use more the preoperatively unpreferred forepaw when tested 1wk after surgery. The overall picture at this stage was little more than that of a shift from the preoperative forepaw preference; but at the retest 8wks after surgery, 8 out of the 9 contralaterally lesioned ss had completely reversed their forepaw preferences - in fact, to the extent of virtually using only the preoperatively unpreferred forepaw. The 9th s, however, showed a clear recovery of the preoperative forepaw preference at the retest carried out 8wks after surgery.

8 ss with 6-OHDA destruction of the nigrostriatal DA system ipsilateral to the preoperatively preferred forepaw retained their forepaw preference when tested 1wk or 8wks after surgery.

6 partially lesioned ss, whose 6-OHDA had practically missed the MFB target, retained their preoperative forepaw preferences irrespective of whether the neurotoxin was administered on the same side as or on the side opposite to the forepaw preferred prior to surgery.

The 6 primary control ss, which had been injected contralaterally with the saline-ascorbic acid vehicle not containing 6-OHDA, also retained their preoperative forepaw preferences when tested 1wk and 8 wks after surgery.

Figure 9 presents graphically the patterns of effective forepaw use exhibited by the four different groups of ss preoperatively, 1wk postoperatively/

postoperatively and 8wks postoperatively.

Before surgery, all ss made more abortive (subthreshold) presses with the predominantly used forepaw than with the unpreferred forepaw. This pattern (that is, more abortive presses with the currently dominant forepaw) was maintained in the postoperative test and retest runs (1wk and 8wks after surgery, respectively) in all four groups of ss. The contralaterally lesioned ss, which had had to reduce or stop pressing with the preoperatively preferred forepaw, exhibited a corresponding drop in the number of abortive presses made with that paw. In Figure 10 is shown a graphical representation of the patterns in which the forepaws were used to make abortive presses preoperatively, 1wk postoperatively and 8wks postoperatively. The pattern of forepaw use is reversed following surgery only in the case of the contralaterally lesioned group. The differences presented in this figure are statistically significant ($p < 0.025$, Wilcoxon test, one-tailed) in the various groups of ss.

All ss with total or near total unilateral nigrostriatal lesion showed a drop in the rate of lever-pressing when tested 1wk after surgery. The drop was statistically significant at the 0.005 lever in the case of the 9 contralaterally lesioned ss (Wilcoxon test, one-tailed) and at the 0.025 level in the case of the ipsilaterally lesioned ss (Wilcoxon test, one-tailed). On the other hand, both the partially lesioned and the vehicle-injected control groups displayed an increase in the rate of lever-pressing when tested 1wk postoperatively, although the increase was not statistically significant.

FIGURE 9:

Mean patterns of effective forepaw use exhibited in the 6-OHDA-lesioned and control groups of ss preoperatively, 1wk postoperatively and 8wks postoperatively. Each column represents the mean number of effective lever-presses executed with the preoperatively preferred (stippled columns) or unpreferred (open columns) forepaw by a group in 50min (two 25min sessions). The bars represent one SD. There was a significant difference between preferred and unpreferred forepaws in all four groups prior to surgery ($p<0.025$ Wilcoxon matched-pairs signed-ranks test, one-tailed). Following surgery the direction of difference was reversed in the case of the group with extensive damage to the nigrostriatal DA system on the side opposite to the preoperatively preferred forepaw (contralateral ss) ($p<0.025$ Wilcoxon test, one-tailed) but not in the case of the group with an ipsilateral lesion (ipsilateral ss) or of the partially lesioned (Control SS I) or vehicle-injected (Control SS II) group. The difference between the forepaw remained significant 1wk and 8wks after surgery in these latter groups of ss in the same direction as before surgery ($p<0.025$, Wilcoxon test, one-tailed).

Abbreviations: pre-op., before surgery; post-op., after surgery.

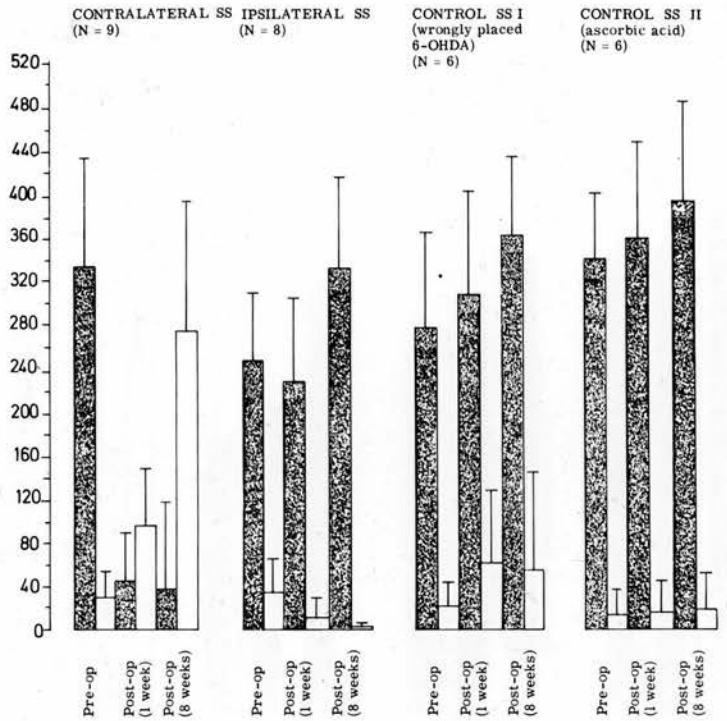
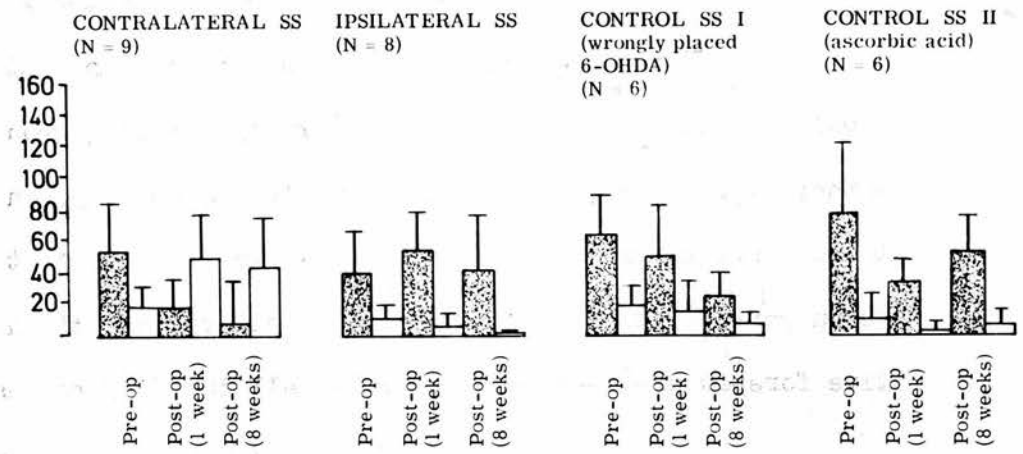

CONTRALATERAL SS
(N = 9)
IPSILATERAL SS
(N = 8)
CONTROL SS I
(wrongly placed
6-OHDA)
(N = 6)
CONTROL SS II
(ascorbic acid)
(N = 6)
520
480
440
400
360
320
280
240
200
160
120
80
40
0
Pre-op
Post-op (1 week)
Post-op (8 weeks)

FIGURE 10:

Mean patterns of abortive forepaw use displayed in the 6-OHDA-lesioned and control groups of ss preoperatively, 1wk postoperatively and 8wks postoperatively. The columns represent the mean number of abortive presses made in each group with the forepaw used for most of the effective presses before surgery (stippled columns) or with the preoperatively unpreferred forepaw (open columns) in two 25min sessions (i.e. in 50min altogether). The bars represent one SD. Note that only in the case of the contralaterally lesioned group of ss was there a reversal of the pattern following surgery; note also that this reversal was still evident when the ss were tested 8wks after surgery. The patterns resemble closely the patterns of effective forepaw use (see Figure 9), and all the differences depicted in the various groups preoperatively, 1wk postoperatively and 8wks postoperatively are statistically significant ($p < 0.025$, Wilcoxon matched-pairs signed-ranks test, one-tailed).

Abbreviations: pre-op., before surgery; post-op., after surgery.


CONTRALATERAL SS
(N = 9)
IPSILATERAL SS
(N = 8)
CONTROL SS I
(wrongly placed
6-OHDA)
(N = 6)
CONTROL SS II
(ascorbic acid)
(N = 6)
160
140
120
100
80
60
40
20
Pre-op
Post-op (1 week)
Post-op (8 weeks)

When retested 8wks after surgery all four groups of ss showed an increase upon their rates at the 1wk postoperative test; but even then the group with a contralateral lesion still performed on the average fewer effective lever-presses than preoperatively over an identical period of time. Rates of lever-pressing are depicted in Figure 11 in terms of the mean number of effective (rewarded) lever-presses executed by each group of ss in 50min (two 25min sessions). In the figure are presented the data from the preoperative and the two postoperative 2-session runs.

Unilateral nigrostriatal lesion did not consistently determine lever preference in the present experiment. Thus the group of ss lesioned on the same side as the preoperatively preferred forepaw did not show a significant difference between the number of effective presses executed on the ipsilateral and the contralateral levers preoperatively, 1wk postoperatively or 8wks postoperatively; although the group lesioned on the side opposite to the preoperatively preferred forepaw showed a significant preference for the ipsilateral lever at the 1wk postoperative test ($p<0.005$, Wilcoxon test, one-tailed), returning to the preoperative degree of difference (not significant) when tested 8wks after surgery. The unlesioned and partially lesioned groups of control ss for their part had a significant preference for the ipsilateral lever prior to surgery ($p=0.025$ Wilcoxon test, one-tailed), and retained this preference at the postoperative test ($p=0.025$, Wilcoxon test, one-tailed). Figure 12 furnishes a graphical comparison between the mean number of effective presses executed on the ipsilateral and contralateral levers by each group of ss in 50min (two 25min sessions) preoperatively, 1wk postoperatively and 8wks postoperatively.

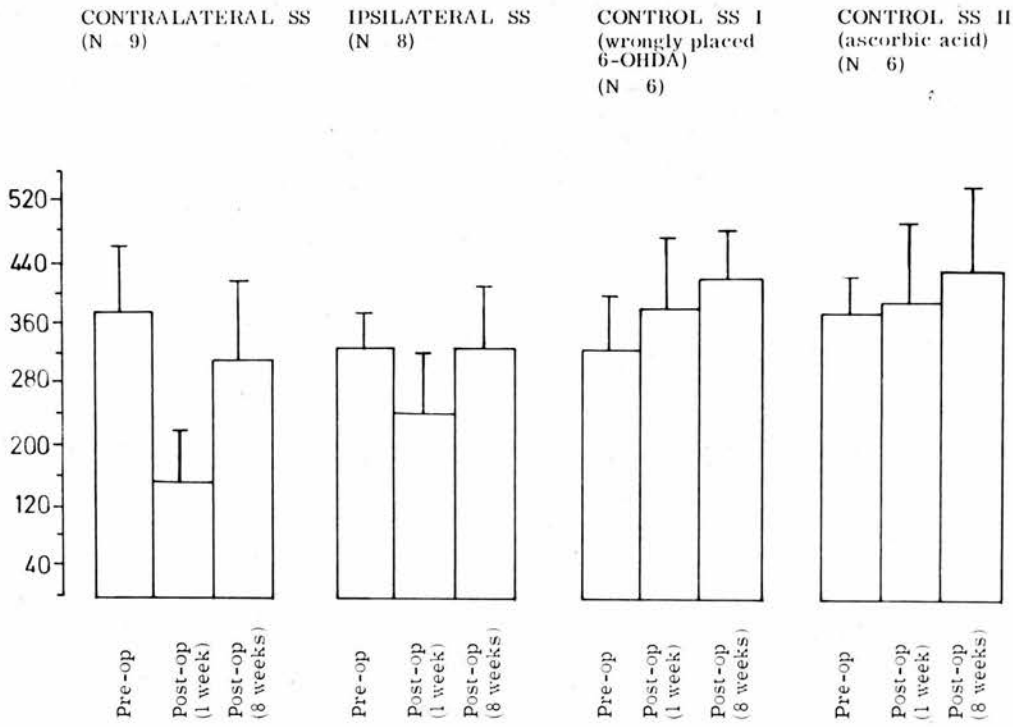


FIGURE 11:

Mean number of effective lever-presses executed in the 6-OHDA-lesioned and control groups of ss in 50min (two 25min sessions) pre-operatively, 1wk postoperatively and 8 wks postoperatively. The bars represent one SD. The lesioned groups of ss showed a significant reduction in number of lever-presses when tested 1wk after surgery ($p < 0.005$ in the controlaterally lesioned group; $p < 0.025$ in the ipsilaterally lesioned group: Wilcoxon matched-pairs signed-ranks test, one-tailed). The increases displayed by the control groups 1wk and 8wks after surgery were not statistically significant. Also there was not a significant difference between the mean number of presses executed in the ipsilaterally or contralaterally lesioned group before and 8wks after surgery.

Abbreviations: pre-op., before surgery; post-op., after surgery.

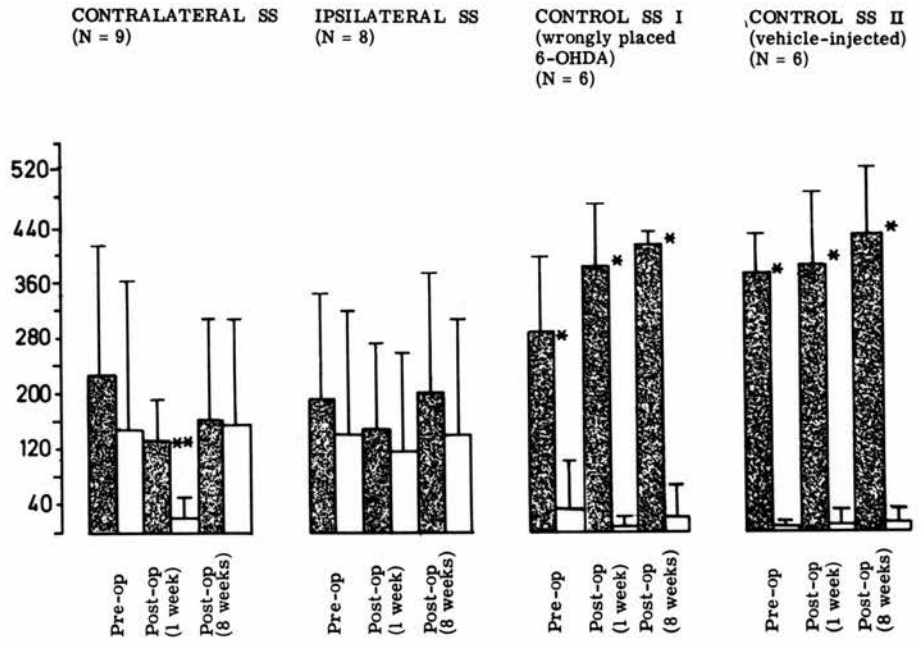


FIGURE 12:

Mean patterns of lever choice exhibited by 6-OHDA-lesioned and control groups of rats in 50min (two 25min sessions) preoperatively, 1wk postoperatively and 8wks postoperatively. The columns represent the mean number of effective presses made by each group on the lever ipsilateral to the injected hemisphere (stippled columns) or the contralateral lever (open columns). Each bar represents one SD.

*p = 0.025

**p = 0.005

Wilcoxon matched-pairs signed-ranks test, one-tailed.

Abbreviations: pre-op., before surgery; post-op., after surgery.

Prior to surgery none of the four groups of ss showed a clear preference for the left or right direction of spontaneous circling. However, at the postoperative test carried out 1wk after surgery the two groups with a total or near-total unilateral lesion displayed a huge enhancement of spontaneous circling and rotated exclusively in the direction of the lesion (ipsiversive circling). Neither direction nor number of rotations was related to the fact that lesion was or was not on the same side as the preoperatively preferred forepaw. At the retest, 8wks after surgery, both lesioned groups were still circling more or less exclusively toward the lesioned side; however, the number of spontaneous rotations performed over an identical period of time (50min) was significantly less than at the 1wk postoperative test ($p < 0.005$ Wilcoxon test, one-tailed).

Neither the control group of ss sustaining a partial 6-OHDA lesion of the nigrostriatal DA system on one side nor the vehicle-injected control group displayed a statistically significant enhancement of the number of rotations or directional preference at the postoperative tests. Figure 13 shows the mean numbers of ipsiversive and contraversive rotations displayed by the four groups in 50min prior to surgery, 1wk after surgery and 8wks after surgery.

4:3(A)($_{ii}$) CATECHOLAMINE ASSAY RESULTS

Table IX shows the % depletions of DA and NE in the various brain regions sampled in each s.

There/

There was more than 94% depletion of DA in the striatum on the lesion side in every one of the experimental ss (ipsilaterally and contralaterally lesioned ss alike). However, as the table shows there were also reductions of striatal NE and of limbic forebrain DA and NE in these animals. The 6-OHDA-injected control group also showed a certain amount of drop in DA and NE contents of the striatum and limbic forebrain on the injected side. The vehicle-injected control ss, on the other hand, had no consistent difference between the two sides in catecholamine contents of the striatum and the limbic forebrain.

There was no significant correlation between the intensity of behavioural impairment and the severity of DA or NE loss in either of the brain regions sampled (Kendall's tau).

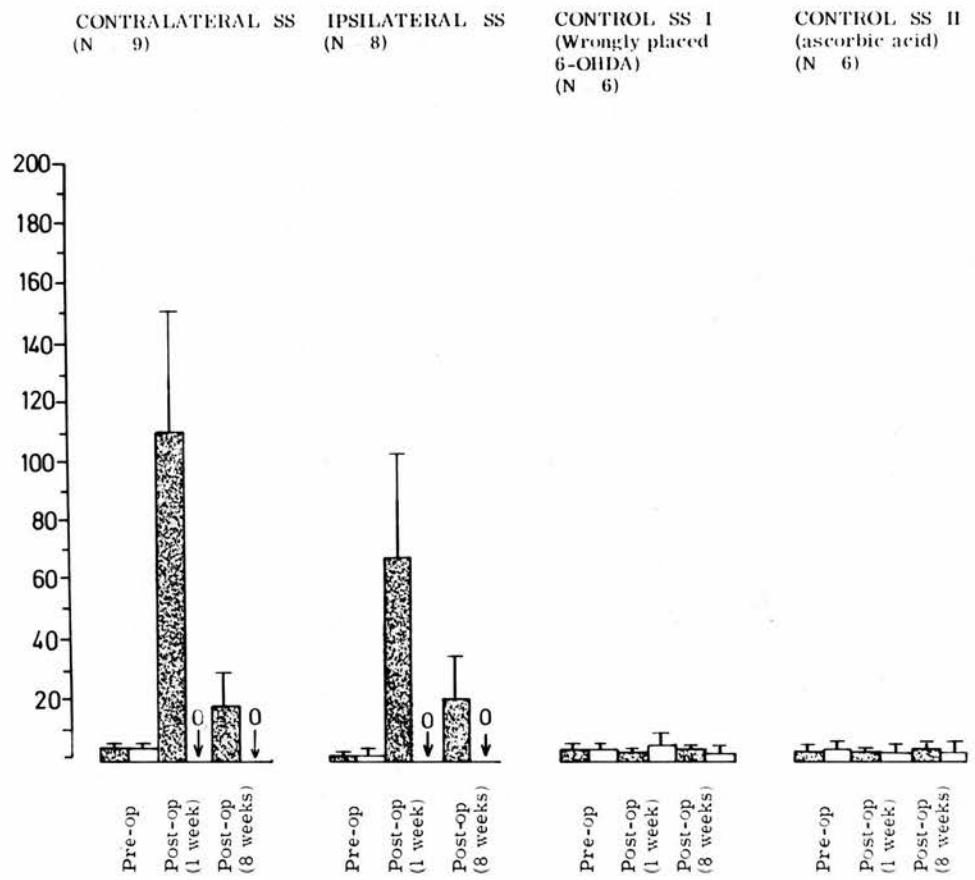


FIGURE 13:

Mean number of rotations performed by the 6-OHDA-lesioned and control groups of ss in each direction in 50min (two 25min sessions in an operant behaviour situation) preoperatively, 1wk postoperatively and 8wks postoperatively. The columns represent the mean number of rotations toward the injected hemisphere (stippled columns) or away from the injected hemisphere (open columns). Each bar represents one SD.

Prior to surgery there was not a significant difference between the left and right directions of circling in any group of ss. The post-operative records showed no significant difference in the control groups. However, the experimental groups of ss (contralateral ss and ipsilateral ss) rotated exclusively toward the lesion side when tested 1wk post-operatively, and this pattern was unchanged 8wks after surgery although number of rotations was significantly less than at 1wk post-surgery in both the contralaterally lesioned and ipsilaterally lesioned groups ($p=0.005$, Wilcoxon's matched-pairs signed-ranks test, one-tailed).

Abbreviations: pre-op., before surgery, post-op., after surgery.

Subject Groups	Subjects	Dopamine		Norepinephine	
		Striatum	Limbic Forebrain	Striatum	Limbic Forebrain
Contralaterally Lesioned (experimental) Group	A	99%	91%	99%	0%
	B	100	100	98	65
	C	100	98	95	23
	D	97	100	78	17
	E	96	94	72	47
	F	99	99	93	15
	G	100	100	89	33
	H	100	100	89	33
	I	98	70	96	75
Ipsilaterally Lesioned (experimental) Group	A	100	99	64	32
	B	99	80	95	77
	C	97	100	87	92
	D	94	85	93	11
	E	97	97	70	67
	F	99	94	82	31
	G	100	100	65	0
	H	99	100	78	0
Partially Lesioned (Control) Group	A	69	58	48	0
	B	2	0	1	0
	C	11	7	20	20
	D	24	0	20	9
	E	47	32	57	0
	F	66	62	75	77
Vehicle-injected (Control) Group	A	0	7	9	7
	B	4	0	0	0
	C	0	4	0	0
	D	0	25	0	0
	E	0	3	0	0
	F	30	9	76	0

TABLE IX:

Percent catecholamine loss in the injected hemisphere of rats given a unilateral 6-OHDA microinjection into the MFB (ipsilateral or contra-lateral to the predominantly used forepaw) and of partially lesioned and vehicle-treated controls.

EXPERIMENT II: SIDE AND GOAL PREFERENCES IN THE T-MAZE

4:2(B) MATERIALS AND METHODS

4:2(B)(i) SUBJECTS

Six male Wistar albino rats weighing between 180g and 200g at the time of surgery constituted the ss for this study. When the animals arrived in the laboratory they were housed in twos in RC1 cages of North Kent Plastic Cages Ltd. in a reverse daylight room, as previously described (2:1). Food and water were constantly available except that (a) food was removed for 48hrs prior to T-maze training in the pre-operative phase, or for 24hrs prior to the postoperative data-gathering phase; (b) water was not available during T-maze sessions.

4:2(B)(ii) BEHAVIOURAL STUDIES

When the animals first arrived in the laboratory they were allowed seven days to get used to the experimental housing conditions before behavioural studies involving them were commenced (2:1). Then they were trained to run a T-maze for food. A detailed description of the training procedure is already given (2:3).

Two data-gathering sessions of 10 runs each were given over the two consecutive days following the completion of training. Then the ss underwent surgery. After surgery they were allowed a test-free recovery period of seven days, and were then given two postoperative test sessions of 10 runs each over two consecutive days.

The categories of data recorded in the data-gathering sessions before and after surgery were: number of times an s chose each arm of the maze, number of times an s rejected each goal-box, and time (in/

(in seconds) taken for each run. A goal-box was adjudged rejected if an s turned fully into the corresponding arm of the maze and then turned away and left without feeding, whether in the process the s got as far as the goal-box or not. Side-preferences and goal-rejections were recorded with the help of a manually operated multi-channelled counting device - each channel being used during any one session for only one kind of information such as choice of left side or rejections of right goal-box.

4:2(B)(iii) SURGERY

All the ss received a microinjection of 6-OHDA (8ug in 4ul isotonic saline containing 0.1% L-ascorbic acid, w/v) into the MFB on the side opposite to the arm of the maze predominantly chosen in the preoperative data-gathering sessions. The ss served as their own controls, being tested before and after surgery. The ss were pretreated intra-peritoneally with pargyline (50mg/kg) and desipramine (25mg/kg) 30min before the administration of 6-OHDA. Details of the surgical procedure have been given earlier (2:5). Following 6-OHDA administration 4min elapsed before the injection cannula was withdrawn, the hole in the skull covered with bone-wax, and the wound sprayed with polybactrin and sutured.

4:2(B)(iv) DISSECTION AND VERIFICATION OF LESION

The ss were sacrificed for the verification of the lesion six weeks after surgery. The animals' brains were quickly removed. Left and right striatal and left and right limbic forebrain samples were dissected out by the procedure described in Chapter 2 (2:9). DA and NE were/

were measured in the samples by the radioenzymatic method of Coyle and Henry (1973) and Palkovitz et al. (1973). For details of the assay method see Chpater 2 (2:12).

4:3(B) RESULTS

4:3(B)(i) T-MAZE BEHAVIOUR

Figure 14a depicts the effect of unilateral nigrostriatal lesion on the side preferences of the ss in a T-maze. The reversal of the pattern of side preferences following surgery was dramatic in these animals, which were all lesioned on the side contralateral to the preoperative side preference.

At the postoperative test the ss circled frequently, and only in the direction of the lesioned nigrostriatal system. When leaving a goal-box the ss turned by the lesion side - never contraversively. In order to return to the start-box, the ss often rotated again, also ipsiversively, at the junction; however, sometimes the ss turned into the stem of the maze straight from the chosen side (contraversive turning), although when they did this they appeared to do it with difficulty.

As Figure 14b(i) shows the postoperative test saw also a marked increase in the number of times the ss turned away from a goal-box without feeding (goal-rejection). It seems interesting to note that most of the rejections were in respect of the goal-box in the pre-operatively unpreferred arm (side) of the maze (Figure 14b(ii)).

The average time taken by an s to run the maze was not significantly altered by the lesion. Figure 14c represents the mean of mean times taken by the ss to run the maze before and after surgery.

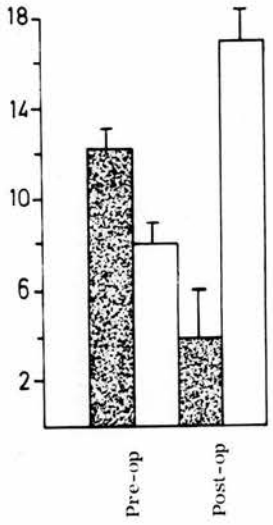


FIGURE 14a:

Side preference in a T-maze before and after a unilateral 6-OHDA microinjection into the MFB of rats. The columns depict the mean number of times the ss chose the ipsilateral (stippled columns) or contralateral (open columns) arm of the maze. Each bar represents one SD. The differences are significant at the 0.025 level (Wilcoxon matched-pairs signed-ranks test, one-tailed).

Abbreviations: Pre-op., before surgery; post-op., after surgery.

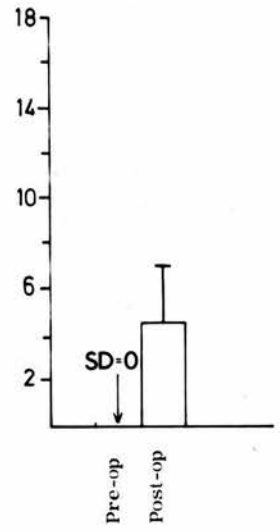


FIGURE 14b(i):

Mean total goal-rejections in a T-maze before and after a unilateral 6-OHDA microinjection into the MFB of rats. The columns represent the mean number of times the ss rejected a goal before or after surgery. Each bar represents one SD. The difference is significant at the 0.025 level (Wilcoxon matched-pairs signed-ranks test, one-tailed).

Abbreviations: Pre-op., before surgery; post-op., after surgery.

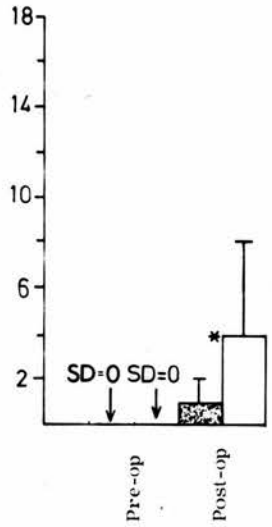


FIGURE 14b(ii):

Mean patterns of goal-rejections in a T-maze before and after a unilateral 6-OHDA microinjection into the MFB of rats. The columns represent the mean number of times the ss rejected the goal-box on the same side as (stippled columns) or opposite to (open columns) the lesion side. Each bar represents one SD.

* p=0.025

Wilcoxon matched-pairs signed-ranks test, one-tailed.

Abbreviations: Pre-op., before surgery; post-op., after surgery.

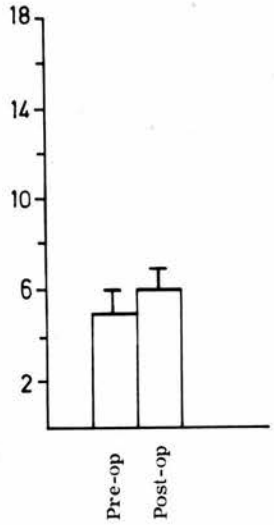


FIGURE 14c:

Mean time taken to run the maze before and after a unilateral 6-OHDA-microinjection into the MFB of rats. The columns depict the mean times (in seconds) taken by the ss to run the maze. The difference is not statistically significant (Wilcoxon matched-pairs signed-ranks test). Each bar represents one SD.

Abbreviations: Pre-op., before surgery; Post-op., after surgery.

4:3(B)(ii) CATECHOLAMINE ASSAY RESULTS

The per cent depletions of DA and NE in the striatum and the "limbic forebrain" of the lesioned hemisphere of the animals used in this study are shown in Table X. From the table it can be seen that all the ss sustained a striatal DA loss of 99% or more in the lesioned hemisphere; however, it may be noted that striatal NE and also limbic DA and NE were depleted as well.

	Dopamine		Norepinephine	
Subjects	Striatum	Limbic Forebrain	Striatum	Limbic Forebrain
A	99%	79%	82%	4%
B	100	87	94	0
*C	100	96	94	15
D	99	96	87	0
E	99	78	100	17
*F	100	100	87	74

TABLE X:

Percent catecholamine reductions in the lesioned hemisphere of rats given a unilateral 6-OHDA microinjection into the MFB opposite to the preoperatively preferred side of a T-maze. These same ss were trained 2wks after surgery to operate levers in a Skinner box for food reward.

*Ss that failed to acquire the operant response.

EXPERIMENT III: OPERANT LEARNING, SENSORIMOTOR PERFORMANCE AND SPACE-RELATED BEHAVIOUR IN THE SKINNER BOX

4:2(C) MATERIALS AND METHODS

4:2(C)(i) BEHAVIOURAL STUDIES

The ss for this experiment were the same ones used in Experiment II. At the end of the second and final postoperative test session the ss were not allowed to feed longer than 30sec at the goal-box, but were instantly removed and placed in a clean two-lever Skinner box prepared in advance for use in operant behaviour training. The training procedure has been described in full elsewhere (2:2).

Throughout the period of training all the food an s had was that obtained by operating the levers in the Skinner box. The ss were not given supplementary feeding outside the operant behaviour training situation; this was because the precise effect of any such extra feeding on the motivation to learn was unknown.

Animals failing to reach the criterion of learning (2:2) by the third day of training were regarded as failing to learn. As for ss that reached criterion in time, they were allowed to go on working for food for a further 30min period. Such animals were tested for 30min about 24hrs later, just to confirm that they had indeed acquired the lever-pressing response. If they displayed retention of the learning, they were adjudged trained and were given a 25min data-gathering (recorded) session in the Skinner box the next day.

The categories of data observed and recorded were: number of effective lever presses made with each forepaw, number of abortive presses made with each forepaw, total number of effective presses made during/

during the session, number of times each lever was effectively depressed, and number of rotations toward or away from the side of lesion. Records were taken with the help of a many-channelled manually operated counting device and a set of electromagnetic counters (2:2).

4:2(C)(ii) VERIFICATION OF LESION

The ss were killed 4wks after the 25-minute-long data-gathering sessions in the Skinner box (4:2(C)(i)), that is, 6wks after surgery (4:2(B)(iii)). The procedures for dissection and verification of lesion have already been described (4:2(B)(iv); 2:9; 2:12).

4:3(C) RESULTS

4:3(C)(i) OPERANT LEARNING AND PERFORMANCE AND SPACE-RELATED BEHAVIOUR IN THE SKINNER BOX

Of the six ss used in the T-maze experiment only four reached the criterion of learning in the Skinner box under the conditions of training (2:2) used in this part of the study. However, as Table XI shows, although three of these ss reached criterion in the third day of training, the fourth s, surprisingly enough, learned in under 20min of the very first training session - a learning time as good as almost any observed with normal (intact or vehicle injected) animals in the author's experience. The learning results are presented in Table XI.

Two of the successfully trained ss displayed, as expected, an exclusive preference for the forepaw ipsilateral to the lesioned nigrostriatal system in the performance of lever presses; but, contrary to expectation, the other two ss showed a clear preference for the contralateral forepaw. What was a strikingly interesting observation in this experiment is that one of the ss preferring the contralateral

forepaw/

forepaw did so to the utter exclusion of the other forepaw and rotated ipsiversively to retrieve every single food pellet procured with a lever press; this rotational tendency was abnormal behaviour and reflected the steep asymmetry between the nigrostriatal systems of the two hemispheres, as was to be confirmed by brain catecholamine assay results. Figure 15a(i) depicts the mean pattern of effective forepaw use exhibited by these ss in the execution of rewarded lever presses. As Figure 15a(ii) shows, the pattern of forepaw use in the performance of abortive (subthreshold) presses was similar to the pattern of effective (rewarded) forepaw use.

Lever preference was not consistently related to the side of lesion. Two ss preferred the lever ipsilateral to the lesion side, but the other two ss chose the contralateral lever most of the time. The mean pattern of lever preference is presented graphically in Figure 15b.

The mean number and the direction of spontaneous rotation recorded in respect of these ss during the session are depicted in Figure 15c. As the figure shows, all the rotations were towards the lesion side, and the number was quite high for a 25min session - compared, for instance, to records obtained in the case of a control group in a previous experiment (refer to Figure 13).

4:3(C)(ii) CATECHOLAMINE ASSAY RESULTS.

All the ss had a striatal DA loss of 99% or more on the lesion side; but striatal NE concentration was also reduced and so were the concentrations of DA and NE in the limbic forebrain of the lesion side. The brain catecholamine assay results have already been presented (Table X) as % depletions in the striatum and the limbic forebrain of the lesion side.

*Subjects Trained	Subjects Reaching Criterion	Days Taken to Reach Criterion
A	A	1
B	B	3
C		
D	D	3
E	E	3
F		

TABLE XI:

Time taken by rats with a two-wk-old unilateral microinjection of 6-OHDA into the MFB to acquire a food-rewarded operant response.

* The ss are the same as those with an identical label in Table X.

A 60min training session followed two hours later by a similar 30-min session constituted one day of training (see 2:2).

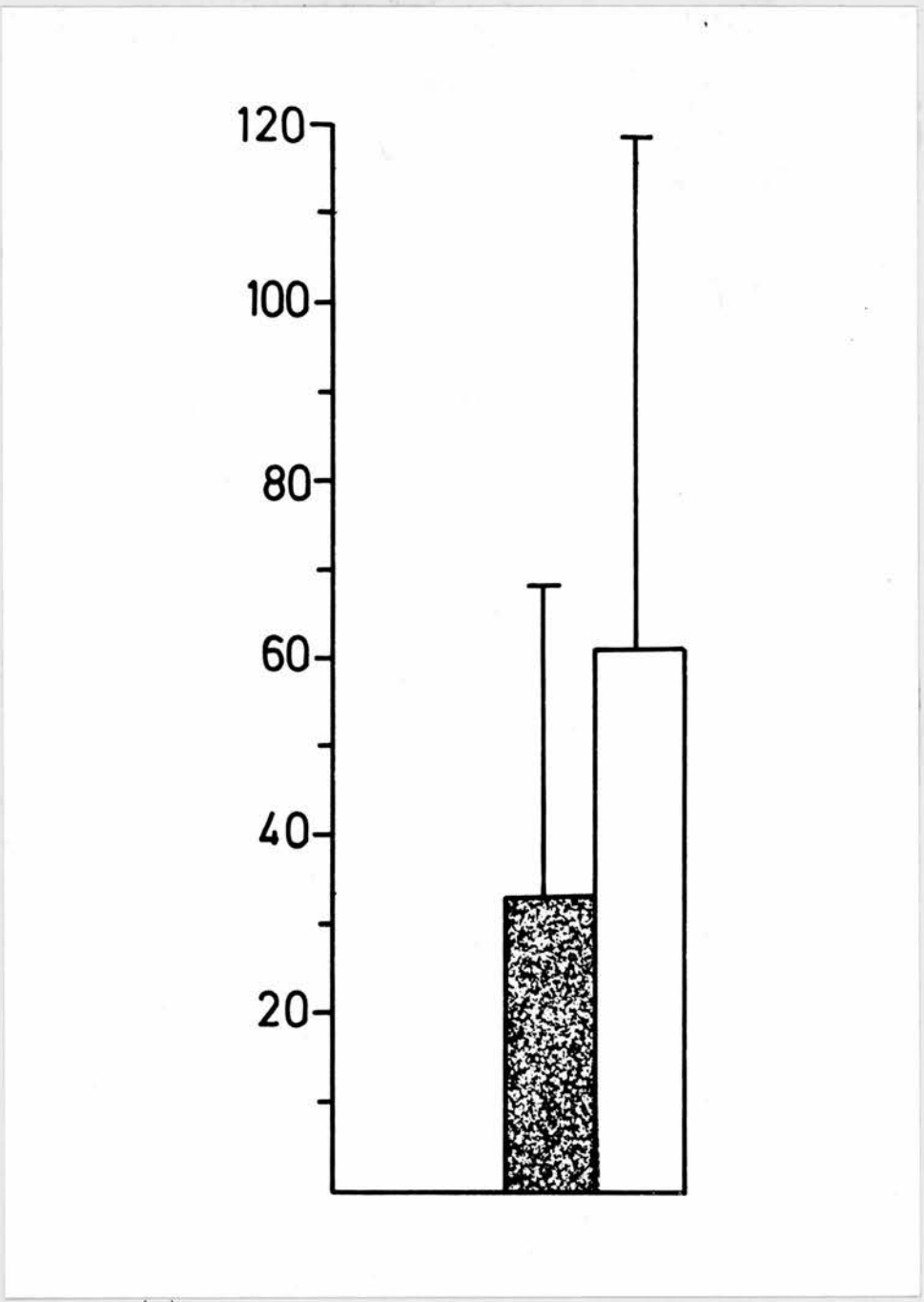


FIGURE 15a(i):

Mean pattern of effective forepaw use displayed by rats trained 2wks after a unilateral 6-OHDA lesion of the MFB to operate levers in a Skinner box for food reward. The columns refer to the mean number of effective lever presses executed with the ipsilateral forepaw (stippled column) or with the contralateral forepaw (open column) in a 25min session. Each bar represents one SD.

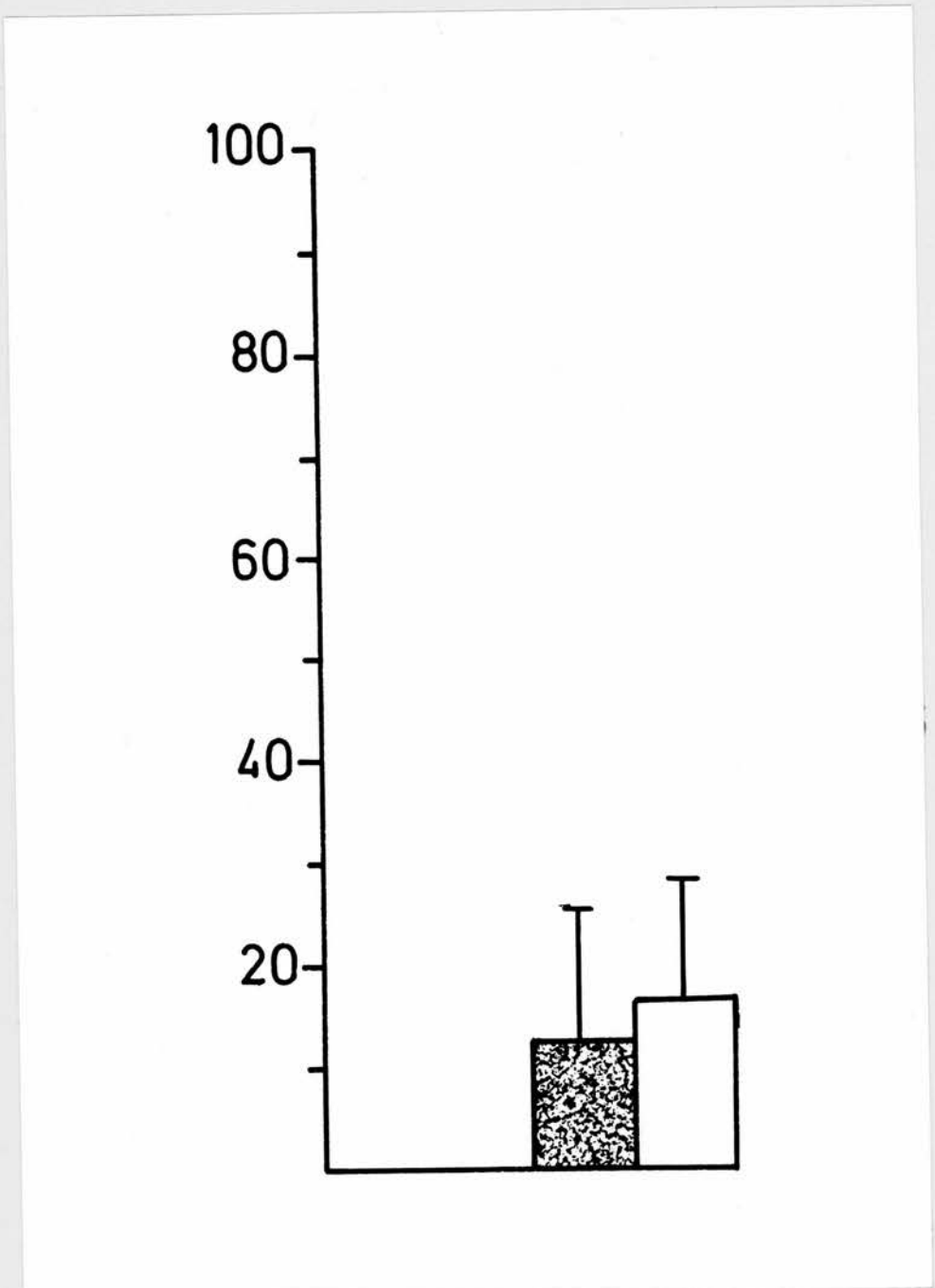


FIGURE 15a(ii):

Mean pattern of abortive forepaw use displayed by rats trained 2wks after a unilateral 6-OHDA lesion of the MFB to operate levers in a Skinner box for food reward. The columns depict the mean number of abortive lever presses made with the ipsilateral forepaw (stippled column) or with the contralateral forepaw (open column) in a 25min session. Each bar represents one SD.

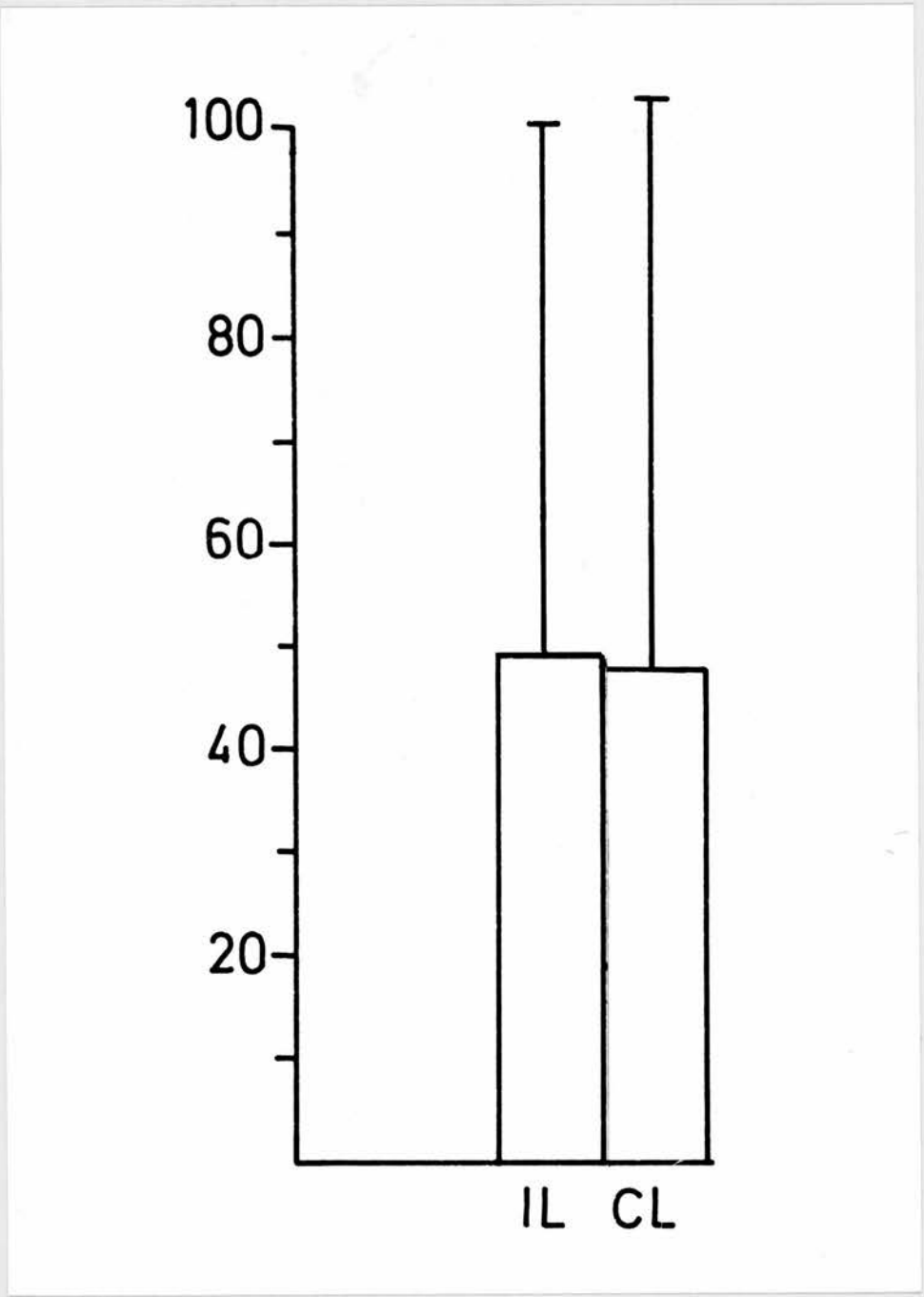


FIGURE 15b:

Mean pattern of lever choice exhibited by rats trained 2wks after a unilateral 6-OHDA lesion of the MFB to operate levers in a Skinner box for food reward. The columns depict the mean number of effective presses executed on the ipsilateral lever or on the contralateral lever in a 25min session. Each bar represents one SD.

Abbreviations: IL, ipsilateral lever; CL, contralateral lever.

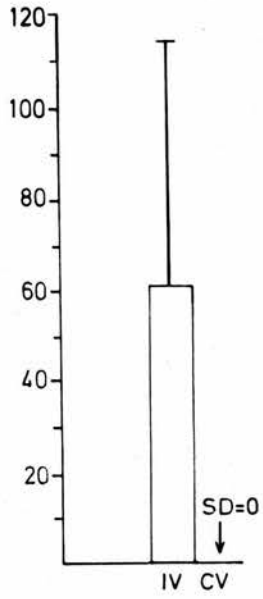


FIGURE 15c:

Mean number of rotations performed in each direction during a 25min operant behaviour session by rats trained 2wks after a unilateral 6-OHDA lesion of the MFB to operate levers in a Skinner box for food reward.

Abbreviations: IV, ipsiversive; CV, contraversive.

4:4 DISCUSSION

4:4(i) EFFECT OF NIGROSTRIATAL LESION ON OPERANT LEARNING

An interesting observation in the operant learning part of the work presented in this Chapter (4:2(C)(i); 4:3(C)(i)) was the failure of two out of six ss to reach learning criterion in the Skinner box in three days of training under the conditions adopted by the investigator. It may be recalled that in a previous experiment (3:3(ii)) two out of seven rats with a twelve-week old unilateral nigrostriatal lesion of the kind used in the present study also failed to learn. The result of the present experiment appears to confirm the suggestion made in discussing the earlier study (3:4(ii)) to the effect that nigrostriatal damage may have had a basic disruptive effect on learning capacity. The failure of the animals to learn may have been due to an impairment of the ability to form a stable association between lever pressing and food availability. Such an interpretation is in line with the results of the discrimination study of Ranje and Ungerstedt (1977) in which rats sustaining bilateral nigrostriatal damage exhibited an impairment of the ability to learn brightness discrimination and spatial discriminatin in an underwater Y-maze. Also supporting the viewpoint that nigrostriatal DA system is involved in learning is the finding by Routtenberg and Holzman (1973) that electrical stimulation of the substantia nigra, pars compacta, during or immediately after a passive avoidance training disrupts retention of the task 24 hrs. later. However, it is known that a unilateral 6-OHDA lesion of the nigrostriatal DA system does not interfere with the acquisition or retention of a passive avoidance task even although the disruptive effect of nigral stimulation on retention is prevented by prior 6-OHDA lesion of the nigrostriatal bundle on the same side as the stimulating electrode (Fibiger, 1977). Fibiger (1977)

concluded that the dopaminergic nigrostriatal bundle is not a critical neural substrate for long-term memory. In the light of the above-mentioned research reports it seems possible that the type of learning task is an important factor in determining whether or not its acquisition or retention is impaired by nigrostriatal damage.

4:4(ii) SENSORIMOTOR PERFORMANCE: LEVER PRESSING ACQUIRED IN THE EARLY POSTOPERATIVE PHASE.

It may be recalled that (a) animals sustaining unilateral 6-OHDA lesion of the nigrostriatal pathway contralateral to the forepaw predominantly used for food-rewarded lever pressing displayed a reversal of forepaw preferences when tested postoperatively (4:3(A)(i)), and (b) that animals acquiring food-rewarded lever pressing for the first time 12 weeks after surgery operated the lever with only the forepaw on the same side as the lesioned nigrostriatal pathway. It was, therefore, predicted that all the lesioned rats reaching criterion in the operant learning part of the work reported in this chapter (4:2(C)(i)) would show a clear preference for the forepaw ipsilateral to the lesioned nigrostriatal pathway. This prediction turned out to be wrong (4:3(c)(i)). Preference for the contralateral forepaw, such as was exhibited by two of the animals, had not been due to failure of the lesion since the catecholamine assay results (4:3(C))ii)) confirm the success of the lesion. Moreover, it had been observed that these ss, as well as those showing preference for the ipsilateral forepaw, rotated exclusively in the direction of the lesion during the operant behaviour/

behaviour session and, in fact, one of the ss which preferred to use the contralateral forepaw rotated (ipsiversively) before retrieving each one of the pellets procured by pushing the lever.

The observation regarding forepaw use by animals acquiring an operant response about 2wks after a unilateral nigrostriatal lesion is difficult to explain. It cannot be, however, that nigrostriatal damage is indifferent to the capacity to use the forepaws, since it has been shown that animals with a unilateral lesion of the nigrostriatal pathway contralateral to the preoperatively preferred forepaw reverse their forepaw preferences whereas animals sustaining an ipsilateral lesion retain their preoperative forepaw preferences (4:3(A)(i)). Also it cannot be that the effect of nigrostriatal damage on forepaw use is an effect confined to already acquired responses, since animals trained for the first time 12wks after surgery operated the lever with virtually only the ipsilateral forepaw in an earlier experiment (3:3(ii)). It is possible then that while nigrostriatal damage does disrupt established sensorimotor habits, and while nigrostriatal damage of long standing (e.g. 12wks) does interefere with the sensorimotor performance of freshly acquired responses, more recent lesions (e.g. 2wk old lesions) are less ubiquitous and, conceivably, less complete in their disruptive effect on the sensorimotor performance of freshly acquired responses. Such an interpretation is out of step with the finding by other investigators (Anden, Bedard, Fuxe and Ungerstedt, 1972; Hokfelt and Ungerstedt, 1969, 1973), that following 6-OHDA microinjection into the MFB degeneration of nigrostriatal DA axon terminals is complete in 48hrs, since this rate of degeneration implies that 2wk old lesions are not different from 12wk old ones in their structural effect on the nigrostriatal/

nigrostriatal DA pathway. However, further work is required to resolve this discrepancy, possibly by determining to what extent the rate of that structural change which is consequent upon 6-OHDA microinjection into the MFB corresponds with the rate at which various behavioural effects are manifested following such a treatment.

4:4(iii) NIGROSTRIATAL DOPAMINERGIC CONTROL OF T-MAZE BEHAVIOUR

The side-preference result of the T-maze experiment (see Figure 14a) is in line with the report of Rothman and Glick, (1976) that a unilateral electrolytic lesion of the caudate nucleus produced a preference for the ipsilateral arm of a T-maze in rats that were free to choose either arm in order to escape electric shock. These authors interpreted their results in terms of lesion-induced asymmetry between the nigrostriatal system of the two hemispheres of the brain. In the present experiment the ss were given a more discrete lesion of the nigrostriatal system through the microinjection of the catecholamine - specific neurotoxin, 6-OHDA, into the MFB. Although the goal that the ss in the present experiment had to run the maze for was food instead of shock escape, the fact that disruption of the nigrostriatal system opposite to the pre-operative side preference completely reversed that preference in every one of the rats used appears to support the view that the result obtained by Glick and co-workers was due to lesion-induced asymmetry between the nigrostriatal system of the two hemispheres.

It may be recalled that in the present experiment the ss displayed a great increase in the number of times a goal was rejected during 20 trials (runs) at the postoperative test. An explanation for this observation/

observation is not readily available, especially since lesion effect on emotionality was not investigated in the present study. It should be noted, however, that most of the postoperative goal-rejections occurred in the arm of the maze less frequently chosen before surgery. This feature of the results cannot be due to any particular dislike for one or the other dish provided at the goal-boxes since rejections of a goal occurred irrespective of which dish was there. A possible explanation is, however, that the observed goal-rejections partly represented rejections of an area in space. The goal-preferences observed in these animals before surgery may well have been associated with a network of external and internal cues which the experimenter failed to pin down, and such cues may have survived when surgery compelled the ss to change their normal (preoperative) side-preference, with the result that they tended to exhibit an enhancement of goal-rejections. The fact that two of the ss did not show this increase in goal-rejections might be reflecting individual differences among the ss in a post-surgery adjustment.

The lack of difference between mean times taken to run the maze before and after surgery might be a bit worrying in view of the known postural and locomotor effects of unilateral nigrostriatal damage (Marshall et al., 1974; Ungerstedt, 1971c), the akinetic effect of bilateral damage (Oltmans and Harvey, 1972; Ungerstedt, 1971a; Zigmond and Stricker, 1972) and the depressant effect on lever-pressing, which has been observed following a unilateral lesion (see Figure 11). In fact, a significant increase in the maze-running time had been expected. However, the large size of the mean of these mean times before surgery suggests that the ss could have benefitted from more practice.

4:4(iv) SENSORIMOTOR PERFORMANCE OF ESTABLISHED REPONSES

In the experiment concerned with sensorimotor function and space-related behaviour in the Skinner box before and after surgery (4:2(A)(ii), 4:3(A)(i)) the groups of ss sustaining an extensive unilateral lesion of the nigro-striatal pathway (associated with 95% or more striatal DA depletion) as a result of 6-OHDA microinjection into the MFB displayed an incapacity to use the forepaw on the side opposite to the lesioned hemisphere when tested 1wk or 8wks postoperatively. As Figure 9 shows, the group lesioned in the hemisphere contralateral to the preoperatively preferred forepaw actually exhibited a reversal of forepaw preferences at the postoperative tests. This finding strongly supports the viewpoint that the nigrostriatal system is involved in the lateralized control of sensorimotor function (Ljungberg and Ungerstedt, 1976; Marshall et al., 1974). It is probably that the nigrostriatal pathway is an integral part of a lateralized neural network which also includes the striatum (Hansing et al., 1968), the pallidum (Levine et al., 1971) and the entopeduncular nucleus (Levine and Schwartzbaum, 1973) and which is concerned with the sensorimotor control of behaviour.

The successfully lesioned groups, but not the unlesioned or partially lesioned controls, also showed at the test 1wk after surgery a drop in the number of effective lever presses executed in a specified amount of time (50min), as compared to their preoperative performance. The reductions in rates of lever pressing were statistically significant in respect to both the contralaterally lesioned ss and the ipsilaterally lesioned ss. In both groups of lesioned ss the decreases in lever-pressing rates may have been partly due to the abnormal enhancement of spontaneous/

spontaneous rotation (Figure 13), which appeared to be involuntary. The decreases may also, however, be related, in some more direct way unidentified in the experiment under consideration, to the akinesia reported by other investigators following bilateral lesions of the nigrostriatal system (e.g. Fibiger, Zis and McGeer, 1973a; 1973b). In the case of the contralaterally lesioned ss, the huge drop in rates may have been due largely to the disruption of the established habit of operating the lever with the spontaneously preferred forepaw, which meant that they had to learn to use the other forepaw. This viewpoint appears to be born out by the fact that at the retest 8wks after surgery these ss displayed a rate of lever pressing that was not significantly lower than the preoperative rate; they seemed to have acquired a certain amount of proficiency in the use of the normally unpreferred forepaw.

In all groups of ss (experimental and control alike), the patterns of forepaw use in the performance of abortive presses were similar to the patterns of effective forepaw use after as well as before surgery (Figure 10). In other words, all ss tended, throughout the study, to make most of their abortive lever presses with the same forepaw that they used to execute their effective presses. Thus when the contralaterally lesioned ss lost the effective use of their preoperatively preferred forepaw they also lost the use of that forepaw in the performance of abortive presses. This observation is supported by the results from other forepaw use experiments (e.g. Figure 7a(ii) and 27) and contradicts the author's expectation that the contralaterally lesioned ss would exhibit an enhancement of the abortive use of their preoperatively/

preoperatively preferred forepaw when tested after surgery. It appears, therefore, that the disruption of sensorimotor control by nigrostriatal damage is an all-or-none effect; in other words, a lesion that is successful in disrupting the effective use of a sensorimotor organ also impairs the ability to initiate abortive efforts to use the organ.

4:4(v) SPONTANEOUS ROTATION VERSUS FOREPAW PREFERENCE IN THE SKINNER BOX: RECOVERY OF FUNCTIONS

As can be seen from the results of Experiment I regarding rotation during operant behaviour sessions (Figure 13), successfully lesioned ss, unlike controls, rotated many more times than preoperatively and only towards the side of lesion, when tested 1wk or 8 wks after surgery. These observations are in agreement with the fact that spontaneous rotation in rats with a unilateral nigrostriatal lesion is ipsiversive (Ungerstedt, 1971e; Anden et al., 1966; Christie and Crow, 1971) and with similar observations in other experiments reported in this thesis (e.g. Figure 7d(i) and 15c).

It should be noted, however, that when the ss were tested 8 wks postoperatively they displayed a much lower rate of spontaneous rotation in the Skinner box than 1 wk after surgery. This is viewed as a sign of recovery and appears in contradistinction to the observed accentuation of forepaw-preference reversal which the contralaterally lesioned ss at the same time displayed in 8 cases out of 9. This divergence between the effects of a nigrostriatal lesion on forepaw used and on spontaneous circling behaviour may have been simply a reflection of different rates of recovery regarding two different functions. This interpretation is supported by the fact that different functions are known to recover at different rates following damage to the lateral hypothalamus (Marshall and Teitelbaum, 1974) or the nigrostriatal system (Marshall et al., 1974). It may,

on the other hand, reflect the involvement of two distinct functional systems that are jointly governed by the nigrostriatal mechanism under different principles. The experiment presented in Chapter 5 was designed partly to test this latter possibility.

4:4(vi) LEVER PREFERENCE IN THE TWO-LEVER SKINNER BOX

In the experiments presented in this chapter lever preference was not consistently related to side of 6-OHDA-induced nigrostriatal lesion (Figures 12 and 15b). This observation confirms the result of an earlier study (Figure 7c), in which three out of five rats trained, 12wks after sustaining a unilateral nigrostriatal damage, to procure food by lever pressing in a two-lever Skinner box of the design used in the present experiments, displayed a preference for the lever on the side opposite to the lesioned hemisphere, whereas the other two ss preferred the ipsilateral lever. This finding is, however, out of line with the suggestion by Glick and Jerussi (1974) that lever preference in a two-lever operant behaviour box is related to asymmetry between the nigrostriatal DA systems of the two hemispheres in such a way that rats tend to choose the lever on the side contralateral to the dominant nigrostriatal DA system. An explanation for this discrepancy might seem to repose in some possible difference in the design of the operant behaviour box used by Glick and Jerussi vis-a-vis that employed in the present series of studies. For example, it may be recalled that the Skinner box used in the present experiments had a common food-tray situated half-way between the two levers (Figure 3); therefore, if an animal operated the right lever to procure food it would be expected to turn to the left to retrieve the food, and if it operated the left lever

it should turn right to reach the food-tray. Thus, although a detailed description of the operant behaviour box used by Glick and Jerussi is not available to the present author, it is conceivable that the provision of only one food-tray midway between the two levers in the present studies may have shrouded any effects of lesion on lever preference which a Skinner box design providing a food-tray beneath each lever might have projected clearly. However, it should be noted that all but one of the control ss used in Experiment I had a clear and consistent preference for one or the other lever throughout the study; in other words, the design of Skinner box used in these studies did not radically destroy all lever preference in the operant behaviour situation. Furthermore, it should be noted that many of the lesioned ss in these experiments habitually rotated fully in the direction of the lesioned hemisphere in order to retrieve the reward of their effective lever presses, when tested postoperatively; yet their lever preferences were clear, and, in the case of the animals lesioned on the same side as the preoperatively preferred forepaw, not reversed after surgery. It seems important that even the rotating ss did not exhibit random lever choice, even although they had to pass the less preferred lever during their rotations.

A reflection on Figure 12 recalls the observation in Experiment I that the group of ss lesioned on the side contralateral to their preoperatively preferred forepaw displayed an enhanced preference for the lever on the same side as the lesioned hemisphere when tested 1wk after surgery. This cannot be due to a direct effect of unilateral nigrostriatal damage on lever preference, since the ipsilaterally lesioned group did not show a similar enhancement of preference for the/

the lever on the side of lesion (Figure 12) despite the fact that the effectiveness of the lesion was comparable between the two groups (Table IX). By the same token the disappearance of all evidence of preference for the lever on the lesion side cannot be regarded as due to recovery from a direct effect of the lesion on lever preference. Indeed, the apparent enhancement of preference for the ipsilateral lever observed in the animals that had lost the voluntary use of their normally preferred forepaw may simply reflect the existence, in the case of these animals, of special performance-related difficulties, possibly of an emotional nature, which were not directly identified in the experiment. Such difficulties may have subsided with time and practice, with the result that the preoperative pattern of lever preference was observed in these animals, as in other groups of ss, at the retest 8wks after surgery.

4:4(vii) SYNOPSIS OF FINDINGS RELATING TO SPATIAL BEHAVIOUR

In the light of the relevant results of the experiments presented in this chapter (Figures 12, 13, 15b and 15c), it seems that rotational behaviour and side preference in a T-maze represent a category of spatial behaviour distinct from that represented by lever preference in a two-lever Skinner box of the design used. This viewpoint appears to some extent supported by the fact that in the T-maze experiment (Figure 14b) some ss displayed an enhancement of goal-rejections when a unilateral nigrostriatal lesion forced them frequently into the preoperatively unpreferred arm of the maze and so toward the goal-box less frequently used before surgery. These ss may have retained their preference for an area in space even after losing the ability to turn freely in that direction./

direction. On the whole, therefore, it seems that rotational behaviour and side preference in a T-maze represent a category of spatial behaviour that is directly influenced by asymmetry between the nigrostriatal systems of the two hemispheres, whereas lever choice in a two-lever Skinner box and goal preference in a T-maze represent a different category of spatial behaviour that is not similarly controlled by the nigrostriatal mechanism.

4:4(viii) INTERPRETATIONAL LIMITATIONS IMPOSED BY THE 6-HYDOXYDOPAMINE LESIONING TOOL.

Unfortunately it has not been possible, through the experiments reported in this chapter any more than in the studies of previous investigators, to demonstrate conclusively whether or not the behavioural functions investigated are actually controlled by the nigrostriatal DA system. This is because, as the biochemical results in the studies show (Tables IX and X), 6-OHDA microinjection into the MFB caused depletions of DA not only in the striatum but also in the limbic forebrain region, and depleted NE as well in these areas. In this regard, it should be noted that although striatal DA depletion was on the whole very severe in the experimental ss, depletion of limbic forebrain DA and striatal NE were also marked. It is not possible, therefore, to play down, on the strength of the present studies, the importance of limbic forebrain DA in the behavioural functions investigated, especially in view of the fact that the nucleus accumbens, which is a limbic structure with a rich supply of DA, is believed by some authors to be involved in co-ordinated movements (Jackson et al., 1974). Also one cannot justifiably disregard off-hand the NE systems supplying the forebrain/

forebrain which were disrupted by 6-OHDA microinjection into the MFB, since their precise roles in the control of behaviour are not fully understood yet. Further work is required to solve these interpretational problems. Two of the experiments reported later in this thesis (Chapter 7) were designed primarily to achieve this objective.

CHAPTER 5

POSTSYNAPTIC DOPAMINE RECEPTOR STIMULATION IN RATS WITH A UNILATERAL NIGROSTRIATAL LESION: NIGROSTRIATAL DOPAMINERGIC CONTROL OF SENSORIMOTOR VERSUS SPATIAL BEHAVIOUR

5:1 INTRODUCTION

5:1(i) NIGROSTRIATAL DOPAMINERGIC INVOLVEMENT IN VOLUNTARY MOVEMENTS

In experimental animals, akinesia, defined as the inability to initiate voluntary movements, is known to result from bilateral lesions of the ventromedial tegmental area of Tsai (Harrison, 1940; Nauta, 1946; Ranson, 1939) or bilateral pallidal lesions (Mettler, 1945). Such lesions interrupt the nigrostriatal DA pathway (Moore, Bhatnager and Heller, 1971; Parent et al., 1969; Ungerstedt, 1971d). Indeed, it has been shown that more or less selective bilateral destruction of the nigrostriatal DA bundle also causes akinesia (Ungerstedt, 1971a). Furthermore, peripheral administration of alpha-methyltyrosine induces akinesia; and this effect is temporarily reversed by L-dopa (Bedard et al., 1970; Larochelle et al., 1971), a drug which in normal (=unlesioned) animals is readily transformed into DA in the striatum (Hornykiewicz, 1966).

Akinesia is one of the cardinal symptoms of Parkinson's disease, and Parkinsonian patients are known to show histopathological changes in the substantia nigra (Hassler, 1938; Tretiakoff, 1919) and an associated DA depletion in the striatum (Ehringer and Hornykiewicz, 1960, Hornykiewicz, 1966). There is little surprise, therefore, that damage to the nigrostriatal DA system is believed to be involved in an important way in the production of akinesia, and possibly of other major symptoms as well, in parkinsonism (Poirier, 1970).

5:1(ii) DOPAMINE RECEPTOR STIMULATION IN THE TREATMENT OF PARKINSONISM

Rats with a relatively discrete (6-OHDA-induced) degeneration of the nigrostriatal DA bundle (Ungerstedt, 1968, 1971b) develop a super-sensitivity to DA agonists in the denervated neostriatum (Ungerstedt, 1971c). Apomorphine, a direct-acting DA receptor stimulating agent (Anden, Rubenson, Fuxe and Hokfelt, 1967; Ernst, 1967) or L-dopa, a DA precursor (Hornykiewicz, 1966), therefore, causes unilaterally 6-OHDA-lesioned animals to rotate towards the intact side (Ungerstedt, 1971e).

It is known, moreover, that peripheral administration of neuroleptics increases the turnover of DA and NE in the brain, whereas drugs which stimulate catecholamine receptors produce a compensatory reduction in catecholamine turnover (Anden et al., 1970; Corrodi, Fuxe and Hokfelt, 1967). Several studies have combined the "6-OHDA rotation model" (Ungerstedt, 1971e) with amine turnover determination to discover new types of possible antiparkinsonian drugs. Examples of such drugs are m-tyrosine (Anden, Butcher, Corrodi, Fuxe and Ungerstedt, 1970), piribedil (Corrodi, Farnebo, Fuxe, Hamberger and Ungerstedt, 1972a) and ergot alkaloids (Corrodi, Fuxe, Hokfelt, Lidbrink and Ungerstedt, 1973). Even apomorphine has been reported to be useful in the treatment of Parkinson's disease (Duby, Cotzias, Steck and Papavasiliou, 1971), although owing to its short-lasting action (Anden et al., 1967; Ernst, 1967) and its tendency to produce marked stereotyped behaviour (Fuxe and Ungerstedt, 1976) this drug is not regularly used as an anti-parkinsonian agent.

5:1(iii)/

5:1(iii) NIGROSTRIATAL DOPAMINERGIC CONTROL OF ROTATION VERSUS LIMB USE: STATEMENT OF HYPOTHESIS

Several studies have already implicated the nigrostriatal DA system in circling (Anden et al, 1966; Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1970; Christie and Crow, 1971) and in side preference in a T-maze (Zimmerberg et al., 1974) and lever preference in a two-lever operant behaviour box (Glick and Jerussi, 1974). In Chapter 4 of this thesis (Figure 13 and 15c) it was shown that rats with a 6-OHDA-induced unilateral MFB lesion rotate more or less exclusively towards the lesion side. It was also shown that rats tend to reverse their forepaw preference if they sustain such a damage on the side contralateral to the preferred forepaw (Figure 9). The results of those experiments suggest that the disruption of the nigrostriatal dopaminergic mechanism was responsible for the observed ipsiversive rotation and contralateral forepaw incapacitation.

The chief aim of the experiment reported in the present chapter was to test the hypothesis that rotational behaviour and forepaw use are governed by the nigrostriatal DA system on the same principles. If ipsiversive rotation and contralateral forelimb dysfunction such as are observed after a unilateral nigrostriatal lesion are both due simply to the loss of DA supply to the denervated striatum, it may be expected that direct stimulation of the striatal postsynaptic receptors of DA, which leads to contraversive rotation, would also restore the ability to use the lesion-incapacitated forelimb. To test this idea apomorphine was used at a dose which preliminary study had shown would elicit contraversive circling in hungry rats with a unilateral nigrostriatal lesion/

lesion and at the same time allow them to push the lever in an operant behaviour box for food reward.

5:2 MATERIALS AND METHODS

5:2(i) SUBJECTS

The ss for the present experiment comprised 15 rats with a unilateral 6-OHDA lesion of the nigrostriatal DA bundle, and 6 vehicle (=saline + ascorbic acid) -injected control rats. 8 of the experimental ss were lesioned on the side contralateral to the forepaw preferred preoperatively in lever-pressing for food in an operant behaviour box; the remaining 7 experimental ss were ipsilaterally lesioned. All the ss were drawn from the animals used in one of the experiments reported in Chapter 4 (see 4:2(A)(i)). These ss were randomly selected at the end of the "retest" operant behaviour sessions carried out in the earlier experiment 8wks after surgery (4:2(A)(ii)).

5:2(ii) BEHAVIOURAL STUDIES

A pilot study had shown that apomorphine can, at the dose of around 0.05mg/kg, produce contraversive circling in a hungry rat with a successful unilateral 6-OHDA destruction of the nigrostriatal DA bundle and still allow the s to work for food reward on a continuous reinforcement schedule when tested in a Skinner box two months after surgery.

The present experiment was carried out in three stages. Stage I consisted in the final 25-min retest session carried out 8wks after surgery in the parent experiment reported earlier (4:2(A)(ii)). Stage II was the heart of the present study and was carried out 1wk after Stage I. It/

It consisted in giving each s an intraperitoneal (ip) injection of apomorphine (0.05mg/kg in 1ml/kg of isotonic saline) following 24hrs of food-deprivation and testing the s in the Skinner box for possible effect on: (a) forepaw preference in effective (rewarded) lever-pressing, (b) forepaw use in making abortive presses, (c) lever preference and (d) rotational behaviour. Stage III was done 1wk after Stage II and consisted in giving each s an ip injection of 1ml/kg of isotonic saline and testing the s in the operant behaviour box exactly as in Stage II. Stages I and III were intended to provide two different baselines for evaluating any possible drug effects that might be observed in Stage II of the experiment.

5:2(iii) VERIFICATION OF LESION

The ss were sacrificed between 1wk and 4wks after Stage III of the present experiment, along with the other ss employed in the parent study reported in Chapter 4. Descriptions of the procedures for dissection and the verification of lesion have already been given (4:2(A)(iv); 2:9; 2:12).

5:3 RESULTS

5:3(i) FOREPAW USE AND SPACE-RELATED BEHAVIOUR

The results of the experiment regarding forepaw use in the execution of effective lever presses are depicted in Figure 16. It can be seen that neither apomorphine nor saline affected the mean pattern of effective forepaw use in the experimental groups or the control group.

The mean patterns of forepaw use in the performance of abortive presses in the various subject groups are shown in Figure 17. It can be/

be seen that, like effective forepaw use, abortive forepaw use was unaffected by apomorphine or saline. Furthermore, the patterns of abortive forepaw use closely resemble the patterns of effective forepaw use in the various groups.

On the other hand, the steady-state patterns of lever choice in the two experimental groups were reversed by apomorphine and also by saline treatment administered 1wk later on (Figure 18). The differences between the two levers were not, however, statistically significant (Wilcoxon matched-pairs signed-ranks test) under either treatment condition or without treatment. Moreover, it should be noted that the effects of apomorphine or saline treatment were different between the two experimental groups. Thus the contralaterally lesioned group operated the lever on the side opposite to the lesion side slightly more than the other lever prior to treatment, but showed a preference for the lever on the same side as the lesion when treated with apomorphine or saline; the mean patterns of lever preference exhibited by the ipsilaterally lesioned group are, for their part, in the direction opposite to the patterns displayed by the contralaterally lesioned group at the various tests. It may be mentioned, though, that lever choice in the control (unlesioned) group was unaffected by apomorphine or saline treatment.

On the other hand, it can be seen from Figure 19 that rotational behaviour was affected in the lesioned groups of ss by the dose of apomorphine used, and also to some extent by isotonic saline given one week after the apomorphine session. Thus whereas the steady-state direction of spontaneous rotation in the lesioned ss was ipsiversive to the damaged nigrostriatal system, apomorphine treatment reversed this/

this pattern clearly; and saline given one week later also elicited contraversive rotation in some of these ss. It should be mentioned that in all the ss which displayed a contraversive circling response to saline treatment, most of that response occurred in one or just a few spells early in the session, while the contraversive circling response to apomorphine came on one or two minutes after treatment and either occupied most of the session to the exclusion of ipsiversive rotation or was interspersed scantily with obviously laboured ipsiversive circles.

5:3(ii) CATECHOLAMINE ASSAY RESULTS

Table XII presents the catecholamine assay results in respect of the contralaterally lesioned, the ipsilaterally lesioned, and the control (vehicle-injected) groups of ss. All the lesioned ss had a reduction of 94% or more in striatal DA content on the side of the lesion. However, striatal NE concentration and the levels of limbic forebrain DA and NE were also markedly reduced on the lesioned side.

There was of course no consistent catecholamine loss on the operated side in the control group.

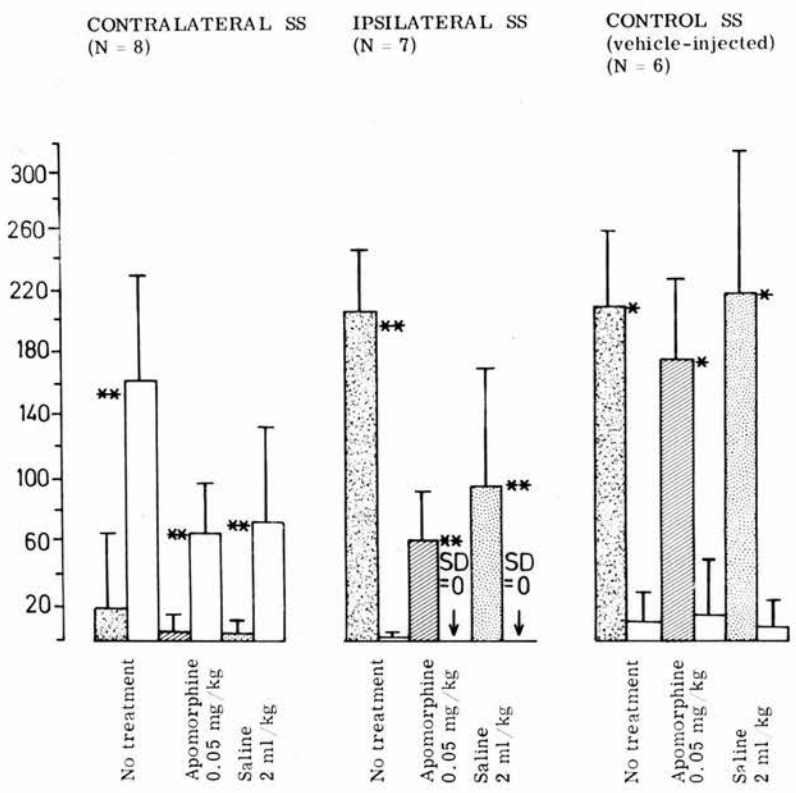


FIGURE 16:

Mean patterns of effective forepaw use displayed by groups of rats with a unilateral 6-OHDA lesion of the nigrostriatal system and by vehicle-injected controls - following i.p. administration of apomorphine or isotonic saline. Each column depicts the mean number of effective lever presses made in a 25-min session with the preoperatively preferred forepaw (stippled, hatched and dotted columns) or with the preoperatively unpreferred forepaw (open columns). Each bar represents one SD.

The postoperative steady-state pattern of forepaw use (labelled "No Treatment" in the graphs) was not affected by apomorphine or saline in any of the groups.

*p = 0.025

**p = 0.005

Wilcoxon matched-pairs signed-ranks test, one-tailed.

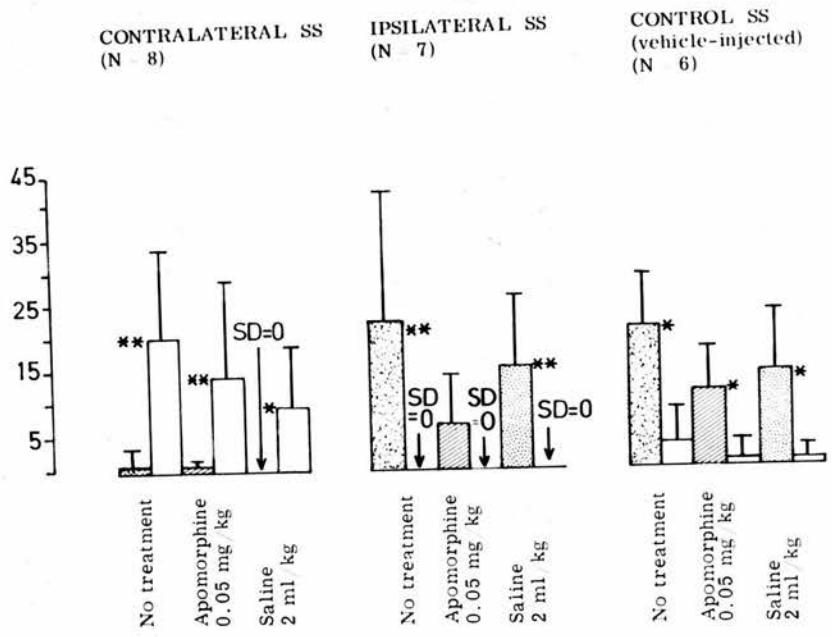


FIGURE 17:

Mean pattern of abortive forepaw use displayed by groups of rats with a unilateral 6-OHDA lesion of the nigrostriatal system and by vehicle-injected controls following i.p. administration of apomorphine or isotonic saline. Each column depicts the mean number of abortive lever presses made in a 25-min operant behaviour session with the preoperatively preferred forepaw (stippled, hatched and dotted columns) or with the preoperatively unpreferred forepaw (open columns). Each bar represents one SD.

Like patterns of effective forepaw use (see Figure 16) the patterns of abortive forepaw use were unaffected by apomorphine or saline treatment in any of the subject groups.

*p = 0.025

**p = 0.005

Wilcoxon matched-pairs signed-ranks test, one-tailed.

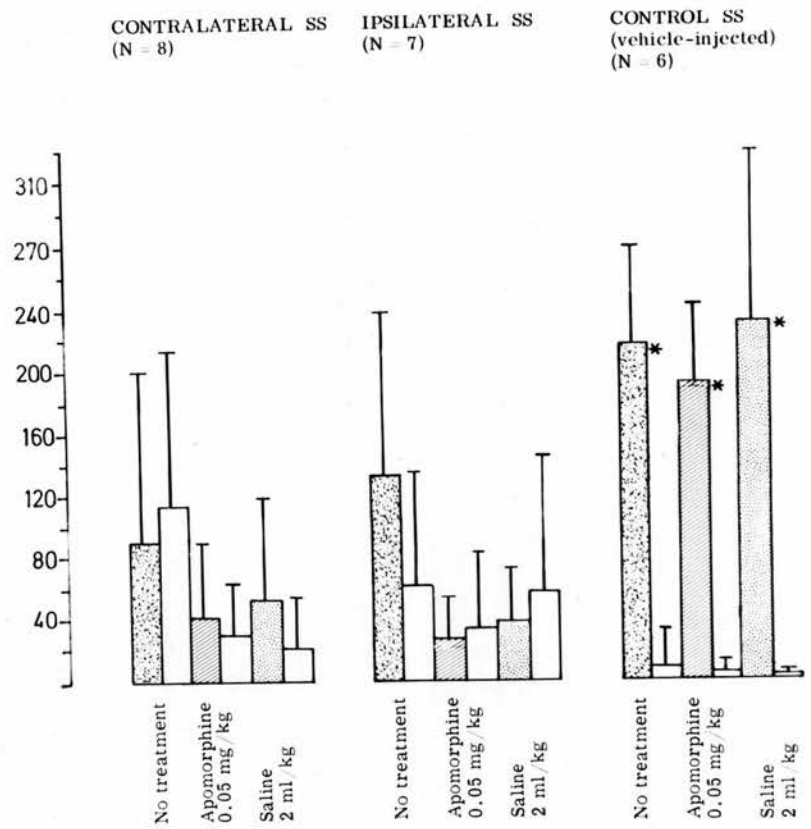


FIGURE 18:

Mean patterns of lever choice displayed in a two-lever Skinner box by groups of rats with a unilateral 6-OHDA lesion of the nigrostriatal system and by a vehicle-injected control group following i.p. administration of apomorphine or isotonic saline. Each column represents the mean number of effective presses made in a 25-min operant behaviour session at the lever on the same side as the lesion (stippled, hatched and dotted columns) or at the contralateral lever (open columns). Each bar represents one SD.

The effect of pharmacological treatment on postoperative lever choice was not consistent between the experimental (lesioned) groups; and no effect was observable in the control group.

*p = 0.025

Wilcoxon matched-pairs signed-ranks test, one-tailed.

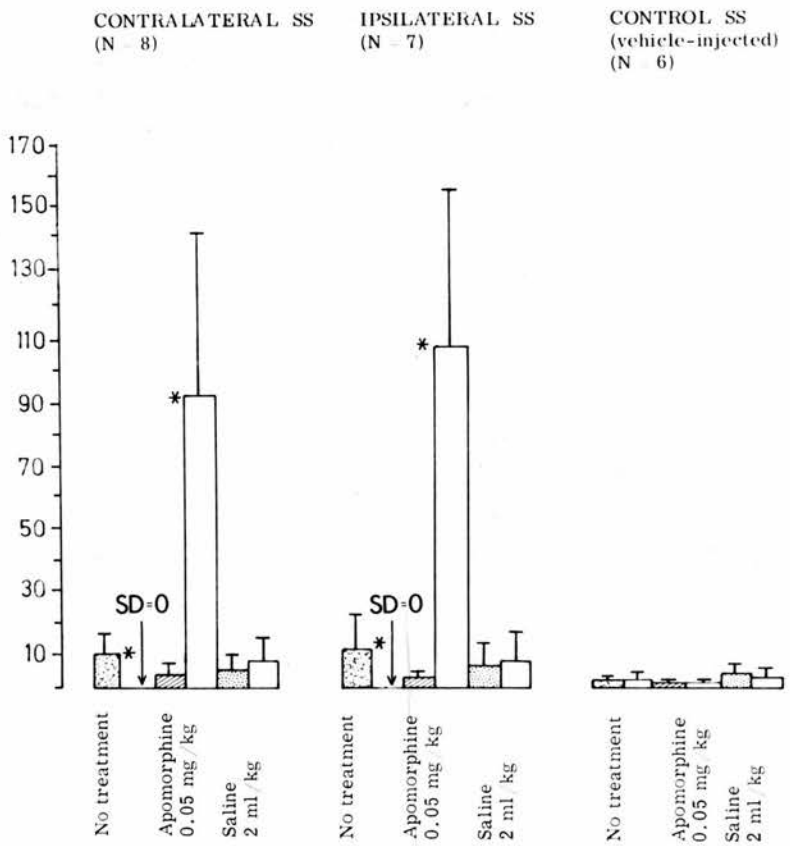


FIGURE 19:

Mean number of rotations to each side performed during a 25-min operant behaviour session by groups of rats with a unilateral 6-OHDA lesion of the nigrostriatal system and by a vehicle-injected control group following i.p. administration of apomorphine or isotonic saline. Each column represents the mean number of rotations toward the lesion side (stippled, hatched and dotted columns) or away from it (open columns). Each bar represents one SD.

Neither apomorphine nor saline significantly affected rotational behaviour in the control group. But apomorphine, and to some extent saline as well, elicited contraversive circling from the lesioned groups.

*p = 0.005

Wilcoxon matched-pairs signed-ranks test, one-tailed.

Subject Groups	Subjects	DOPAMINE		NOREPINEPHINE	
		Striatum	Limbic Forebrain	Striatum	Limbic Forebrain
Contralaterally Lesioned (experimental) Group	A	99%	91%	99%	0%
	B	100	100	98	65
	C	100	98	95	23
	D	97	100	78	17
	E	96	94	72	47
	F	99	99	93	15
	G	100	100	89	33
	H	98	70	96	75
Ipsilaterally Lesioned (experimental) Group	A	100	99	64	32
	B	99	80	95	77
	C	97	100	87	92
	D	94	85	93	11
	E	99	94	82	31
	F	100	100	65	0
	G	99	100	78	0
Unlesioned (control) Group	A	0	7	9	7
	B	4	0	0	0
	C	0	4	0	0
	D	0	25	0	0
	E	0	3	0	0
	F	30	9	76	0

TABLE XII

Percent catecholamine reductions in the injected hemisphere of 6-OHDA-lesioned and control ss used in the experiment presented in Chapter 5.

5:4 DISCUSSION

5:4(i) POSTSYNAPTIC DOPAMINE RECEPTOR STIMULATION: SENSORIMOTOR FUNCTION VERSUS ROTATIONAL BEHAVIOUR

As Figure 19 shows, the dose of apomorphine used in this study was enough to elicit contraversive rotation in the experimental ss. This dose (0.05mg/kg) at the same time allowed the ss to stop in-between bouts of drug-induced circling to push a lever for food. The stimulation of dopaminergic postsynaptic receptors failed, however, to restore in the contralaterally lesioned ss the use of their preoperatively preferred forepaw or to enhance in the ipsilaterally lesioned group the use of the less preferred forepaw (Figure 16). In view of these results it seems that the control of forepaw use which was lost following nigrostriatal pathway lesion is not simply a matter of dopaminergic postsynaptic receptor stimulation, although drug-induced contraversive rotation - and probably also spontaneous ipsiversive circling - such as is associated with unilateral nigrostriatal pathway damage would appear to be dependent upon the relative activities on the postsynaptic receptors of the two nigrostriatal systems (Ungerstedt, 1971c; 1971e). These results do not necessarily detract from the importance of the nigrostriatal DA system in the control of forepaw use - or, for that matter, in sensorimotor control. What is underlined by the difference in the observations regarding rotational behaviour and forepaw use in this experiment is that these two distinct functions appear to be governed on different principles. It is hereby proposed that whereas direction of circling in animals with a unilateral nigrostriatal lesion is determined by the relative postsynaptic receptor activities between the two sides, the impairment of sensorimotor function in these animals is/

is due to the loss of an essential link in the neural transmission chain controlling this function. The hypothesised interpretation of nigrostriatal dopaminergic control of rotational behaviour appears to find some support in the report that a unilateral nigrostriatal lesion leads to increased accumulation of glycogen in the ipsilateral striatum (Hoffman, Toon, Kleinman and Heller, 1973). It may, therefore, be that postsynaptic receptor stimulation by endogenous DA is necessary for efficient utilization of carbohydrates for energy production in the striatum, with the result that a unilateral nigrostriatal lesion means reduced energy availability and hence lower steady-state activity in the ipsilateral striatum. The hypothesised role of endogenous DA in striatal energy mobilization may be complemented by a similar DA action at other brain sites, notably the DA-rich mesolimbic area. As Table XII shows unilateral 6-OHDA microinjection into the MFB resulted in a substantial depletion of ipsilateral mesolimbic ("limbic forebrain") DA as well as ipsilateral striatal DA. Kelly and Moore (1976) have shown that bilateral 6-OHDA lesion of the nucleus accumbens blocks the ipsiversive rotation produced by amphetamine and enhances apomorphine-induced contralateral circling. It may be that the strong rotations observed in the present experiment were due to the fact that unilateral MFB lesion produced asymmetries in the striatum and the mesolimbic area in the same direction, just as the model proposed by Kelly and Moore (1976) would predict. According to Kelly and Moore, both the striatal and mesolimbic DA systems are involved in behavioural arousal, but whereas asymmetry between dopaminergic activities in the two striata determines the direction of rotation, the role of mesolimbic DA is to mediate its intensity. It would appear that the net effect of unilateral 6-OHDA lesion of the MFB on rotational behaviour may be likened to the tendency of a bus loaded only on one side to go toward the lighter side when it is set in motion.

As regards the transmission-chain hypothesis of the contribution of the nigrostriatal system to sensorimotor control, it is interesting to recall that this neural connection is part of the extrapyramidal system - a network associated with sensorimotor control. Interruptions of this network have been shown to produce sensorimotor loss, whether they occur at the level of the striatum (Hansing et al., 1968) or the pallidum (Levine and Schwartzbaum, 1973; Levine et al., 1971). Although the precise functional organisation of the extrapyramidal system, including the nigrostriatal connection, is not fully understood yet, it should not be surprising if a lesion at the nigrostriatal level, like at other levels of the extrapyramidal network, causes sensorimotor dysfunction owing to a break in a functional chain.

5:4(ii) CLINICAL IMPLICATION

The above-suggested analysis of nigrostriatal involvement in rotational behaviour and sensorimotor control has an interesting implication for the treatment of the neurological disorder of parkinsonism. Drugs used in the treatment of Parkinson's disease are frequently dopaminergic agonists (e.g. L-Dopa) or anticholinergic agents (e.g. benzatropine). In this regard it will be mentioned that DA is believed to exert a tonic depressant action on a significant proportion of cholinergic neurons in the striatum (Bloom, Costa and Salmoiraghi, 1965; Cannon, 1970; McLennan and York 1967) and the action of anticholinergic agents would appear to be functionally similar to this kind of effect. We have, however, seen from the results of the present experiment that the therapeutic value of dopaminergic postsynaptic receptor stimulation does not extend to the restoration of the capacity to use a limb rendered "out of use" by a nigrostriatal pathway lesion, although such a treatment elicits contraversive rotation in unilaterally lesioned animals. It is known that rotational behaviour has been used as the behavioural index of therapeutic value in the development of new antiparkinsonian drugs (Anden et al., 1970; Corrodi et al., 1972; Corrodi et al., 1973; Fuxe and Ungerstedt, 1976). But the outcome of the present study seems to show that the functional replenishment of striatal DA as a treatment for the animal model of parkinsonism does not really cure a basic sensorimotor deficit associated with this disorder, although the loss relating to arousal seems to be supplied. It may be that the treatment of parkinsonism will advance better if we recognise that the inability to initiate voluntary movement, which is associated with/

with it (Poirier, 1970), is more than just an impairment of the arousal component of behaviour, and if we therefore look for a way to deal with the loss of sensorimotor control as a distinct deficit.

5:4(iii) NIGROSTRIATAL ASYMMETRY AND LEVER PREFERENCE

From Figure 18 it can be seen that apomorphine treatment had not a consistent effect on lever preference. Thus apomorphine caused the group of experimental ss with a lesion on the side opposite to the preoperatively preferred forepaw (4:2(A)(ii)) to appear to prefer somewhat the lever ipsilateral to the lesion side, whereas a similar treatment appeared to produce in the group lesioned on the same side as the preoperatively preferred forepaw (4:2(A)(ii)) a slight preference for the lever situated contralaterally to the lesion side. This differential effect of treatment in the two experimental groups cannot reasonably be due to the fact that the former group had had to reverse their forepaw preferences after surgery whereas the latter group had retained their preoperative forepaw preferences (Figure 9), since (a) the postoperative forepaw preferences were established in both groups by the time of treatment (9wks post-surgery) and (b) neither group displayed any effect on forepaw use following apomorphine administration. However, the differential effect of apomorphine treatment on lever preference in the two groups is reminiscent of the finding that only ss under stress as a result of the disruption of their habitual forepaw preference displayed a significant effect on lever choice following surgery (4:4(vi)). In the light of the earlier finding, it seems reasonable to conclude that the observed apomorphine effect on lever preference in the present experiment was due to drug-induced stress rather than a genuine influence of nigrostriatal asymmetry on lever choice in a two-lever Skinner box of the design used.

CHAPTER 6

EFFECTS OF PHARMACOLOGICAL BLOCKADE OF DOPAMINE RECEPTORS ON INGESTIVE BEHAVIOUR AND BODY WEIGHT REGULATION

6:1 INTRODUCTION

6:1(i) INGESTIVE BEHAVIOUR AND BODY WEIGHT REGULATION FOLLOWING NIGROSTRIATAL DAMAGE

Several clearly demonstrable acute and residual dificits which relate to ingestive behaviour are known to result from bilateral lesions which disrupt the nigrostriatal system (Fibiger, Zis and McGeer, 1973a, 1973b; Marshall and Teitelbaum, 1973; Marshall et al., 1974; Oltmans and Harvey, 1976; Ungerstedt, 1971a; Zigmond and Stricker, 1972). It is known also that 6-OHDA-induced lesion of the nigrostriatal pathway on one side causes a chronic reduction in body weight (Baez et al., 1977; see also Figure 6), in non-prandial drinking and in drinking induced by water deprivation or by experimentally engendered dehydration (Baez et al., 1977). In Chapter 3 it was shown, moreover, that animals sustaining a unilateral 6-OHDA lesion of the nigrostriatal bundle exhibit a dramatic enhancement of food spillage (Table V).

6:1(ii) PHARMACOLOGICAL REPRODUCTION OF THE EFFECTS OF NIGROSTRIATAL DAMAGE ON INGESTIVE BEHAVIOUR

Attempts have been made in several laboratories to reproduce, through interfering pharmacologically with the nigrostriatal DA system, those ingestive and other deficits that are associated with actual nigrostriatal damage. In one such attempt, haloperidol, a drug which selectively blocks central DA receptors (Anden et al., 1970) did, at a dose of 0.17mg/kg, reduce the amount of water drunk by animals after deprivation/

deprivation (Fisher, 1973), although some other investigators (Nielson and Lyon, 1973) failed to obtain a similar depression of post-deprivation water intake through the administration of pimozide, another selective blocker of DA receptors (Anden et al., 1970). More recently, Zis and Fibiger (1975) observed no significant effect of haloperidol (0.2mg/kg) or pimozide (0.45mg/kg) on 1hr water intake or 2hr food intake following 24hrs of water- or food-deprivation. These authors, however, found in their haloperidol- and pimozide-treated rats a number of regulatory deficits, such as; drinking less than controls when food was absent or when a systemic injection of hypertonic saline was administered, and eating less than controls in reponse to systemic injection of insulin.

The two experiments reported in the present chapter constitute a further attempt to reproduce, through pharmacological blockade of DA receptors, the effects of nigrostriatal damage on ingestive behaviour and body weight regulation. In one of these experiments (6:2(A); 6:3(A)), the effects of chronic haloperidol treatment at a moderately high daily dose were investigated with regard to food intake, food spillage, and body weight - under conditions of unlimited access to food and of food deprivation. In the other experiment (6:2(B); 6:3(B)) a very high dose of haloperidol was repeatedly administered over a period of three days and the effects of this treatment on ad lib. water and food intake, food spillage and body weight were observed. The rationale behind the adoption of these particular measures - food and water intake, food spillage and body weight - in the investigation of ingestive behaviour and body weight regulation has already been presented, (3:1(vi)).

EXPERIMENT I:/

EXPERIMENT I: FEEDING AND BODY WEIGHT REGULATION DURING AND AFTER CHRONIC TREATMENT WITH A MODERATELY HIGH DOSE OF HALOPERIDOL.

6:2(A) MATERIALS AND METHODS

6:2(A)(i) SUBJECTS

The ss for this experiment were 12 male Wistar albino rats, weighing between 150g and 175g at the start of the experiment. Throughout the study the ss were housed individually in R1 cages of North Kent Plastic Cages Ltd., in a reverse daylight room. For further more general information regarding the ss and the experimental housing conditions see 2:1.

The ss had an unlimited access to food and water, except that (a) food and water were not available during 1hr of data-collection each day (2:4), and (b) food was removed for 24hrs when the animals' reactions to food deprivation were being investigated (6:2(A)(ii)).

6:2(A)(ii) PROCEDURE

The general data-gathering procedure is the same as described in the chapter on techniques (2:4). The present experiment may be viewed as progressing through three stages as follows: pretreatment, treatment and post-treatment stages of recorded observation. At the end of a period of undisturbed orientation in the laboratory housing situation, as already described (2:1), recorded observation commenced with the provision of known amounts of water (100ml) and food (100g) and the measurement of the body weights of the ss. The following day records were taken as follows: amount of water missing from the water bottle, amount of food missing from the food-hopper, amount of food spilled, and body weight. After the records were taken the ss were returned to clean/

clean cages that had fresh supplies of water and food; and this concluded the first of the daily data-gathering sessions. Five such sessions were carried out in the pretreatment stage of the experiment.

In the treatment stage, six experimental ss were treated daily with haloperidol at the dose of 1.0mg/kg in 1ml/kg of isotonic saline, whereas six controls received a comparable volume of bare isotonic saline. The injections were given intraperitoneally at the end of the data-gathering session; and the initial treatment occurred, of course, at the end of the fifth and final pretreatment data-gathering session. There were 25 data-gathering sessions in the treatment stage of the experiment. These data-gathering sessions were identical to the pretreatment sessions except for the injection of ss in the treatment sessions.

On the 15th day of the treatment stage, all the ss were deprived of food for 24hrs to permit the investigation of their reactions to food deprivation with regard to water and food intake, food spillage and body weight.

The post-treatment stage of the experiment lasted for five days and was completely free from treatment; not even isotonic saline was administered. As in the earlier stages, data-gathering sessions in the post-treatment stage included measurements of water and food intake, food spillage and body weight.

6:3(A) RESULTS

For purposes of analysing and presenting the results, the data from the experimental and control groups are compared for the most part for/

for periods of five days in respect of the treatment schedule in which the experimental ss received a daily haloperidol dose of 1mg/kg for 25 days.

Owing to irregularities occurring in the measurements of water consumption in this treatment schedule the data relating to that aspect of ingestive behaviour were discarded. However, body weight, food spillage, food intake and faeces passed were carefully measured, and the data relating to these variables are presented here.

6:3(A)(i) BODY WEIGHT

There was not a significant difference between the two groups of ss in the amount of weight gained or in mean body weight over the 5-day period just preceding the commencement of pharmacological treatment (Mann-Whitney U test). Also the Mann-Whitney U test did not reveal a significant difference between the two groups in the amount of weight gained during the following periods in the treatment phase: days 0-5, 5-10, 10-15 and 17-20. The weight loss sustained in the 24hrs of food deprivation occurring between the 15th and 16th days of treatment was similar in the two groups of ss, as was the weight recovery achieved in 24hrs following food restoration. However, by the 20th day of treatment haloperidol was beginning to depress the rate of body weight increase. The weight-depressant effect of chronic haloperidol administration was clearly evident when the amounts of weight gained from the 20th to the 25th days of treatment were compared between the haloperidol-treated (experimental) and saline-treated (control) groups of ss; the difference was statistically significant ($p < 0.02$, Mann-Whitney U test, two-tailed). After the cessation of treatment, the rate/

rate of weight increase quickly returned to normal in the experimental group. Thus statistical analysis (Mann-Whitney U test) of the amount of weight gained in the five days immediately following the end of the treatment phase did not reveal a significant difference between the two groups of ss. Table XIII shows the mean increase in body weight displayed by the experimental and control groups in the various stages of the study. The mean weights recorded in the two groups from day to day throughout the experiment are depicted side by side in Figure 20.

6:3(A)(ii) FOOD SPILLAGE

Haloperidol treatment did not increase food spillage associated with the process of eating. As a matter of fact, the spillage of food was significantly less in the haloperidol-treated (experimental) than the saline-treated (control) group in the first 5 days of treatment ($p<0.05$, Mann-Whitney U test, two-tailed). There was not a significant difference between the two groups prior to the commencement of treatment, or after the cessation of treatment, or in any of the following periods in the treatment phase: days 5-10, 10-15, 16-17, 17-20 and 20-25. There was also not a significant difference between the two groups in food spillage during 1hr of feeding following 24hrs of food deprivation. All statistical analysis of data regarding food spillage was by the Mann-Whitney U test. Food spillage was analysed, for all stages of the study, in terms of the ratio of amount of food spilled to amount removed from the food-hopper in the process of feeding. The rationale for this measure of food spillage has already been presented (3:3(i)). Table XIV shows the means of these ratios in respect of both the experimental and control groups of ss.

Periods		Experimental Group of ss (N=6)	Control Group of ss (N=6)
Pretreatment Days	5-0	22 ± 5 grams	23 ± 7 grams
Treatment Days	0-5	18 ± 8	19 ± 7
Treatment Days	5-10	21 ± 6	26 ± 4
Treatment Days	10-15	17 ± 4	21 ± 5
Treatment Days	15-16	-25 ± 4	-25 ± 1
● Treatment Days	16-17	23 ± 4	22 ± 5
■ Treatment Days	17-20	12 ± 5	16 ± 5
*Treatment Days	20-25	7 ± 12	19 ± 4
Post-treatment Days	0-5	20 ± 8	22 ± 3

TABLE XIII

Means (±SDs) of weight gained over various periods by rats chronically treated with a moderately high dose of haloperidol (1mg/kg/day for 25 days) and by saline-treated controls.

* $P<0.02$ (Mann-Whitney U test, two-tailed).

● 24hrs of food deprivation.

■ 24hrs following food restoration.

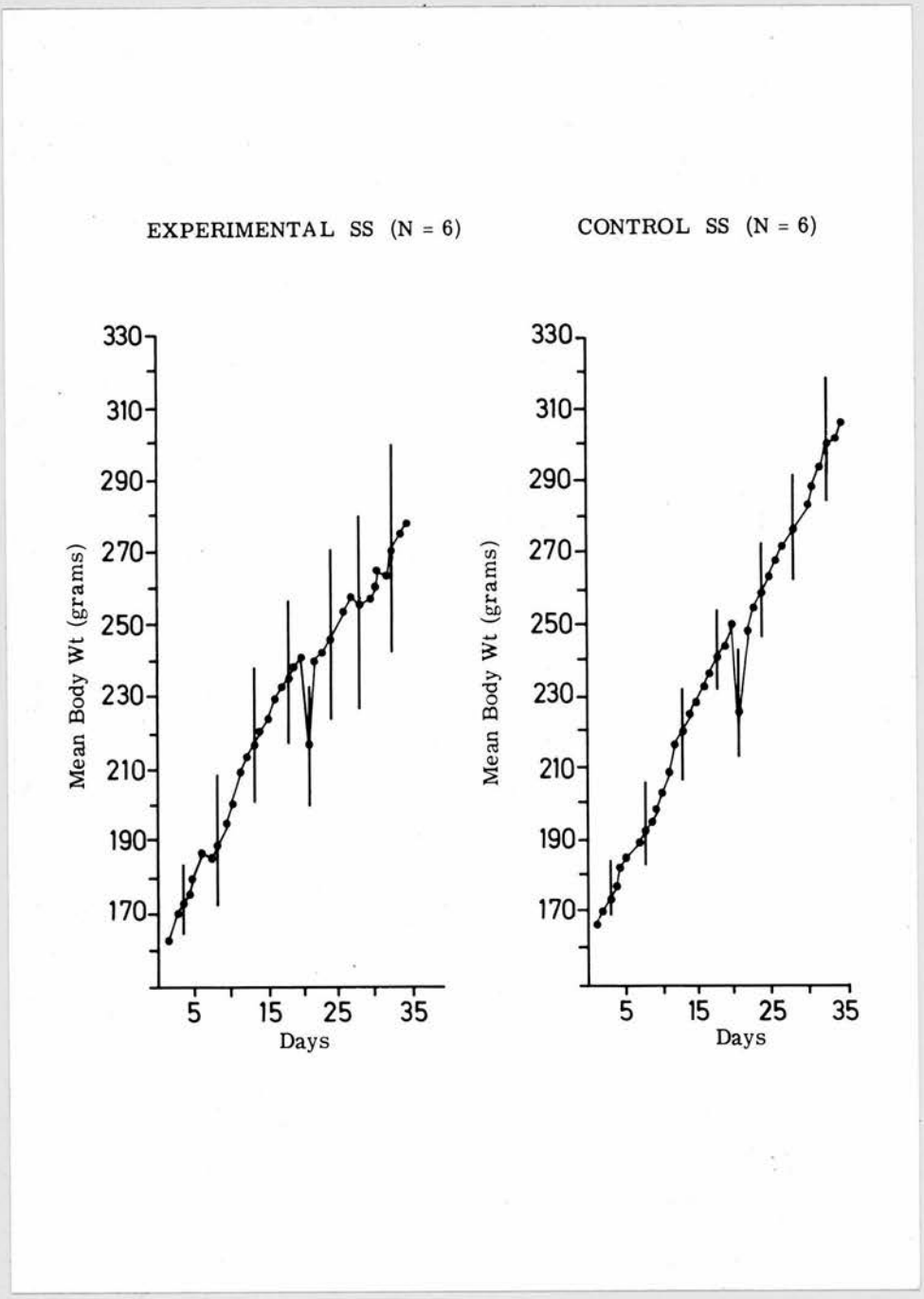


FIGURE 20:

Mean body weights displayed from day to day by rats chronically treated with a moderately high dose of haloperidol (1mg/kg/day for 25 days) and by saline-treated controls. The two groups of ss were similar in mean body weights prior to the commencement of treatment and until about the 17th day of treatment. By the 20th day of treatment, however, the haloperidol-treated group were showing marked deficits in body weight relative to the control group. The bars represent the SDs at the points in time indicated. The SDs were computed for each day of the study; for the sake of clarity, however, only a few are represented in the graph.

Periods		Experimental Groups of ss (N=6)	Control Group of ss (N=6)
Pretreatment Days	5 - 0	0.14 ± 0.02	0.15 ± 0.04
*Treatment Days	0 - 5	0.12 ± 0.04	0.17 ± 0.05
Treatment Days	5 - 10	0.11 ± 0.03	0.13 ± 0.04
Treatment Days	10 - 15	0.11 ± 0.02	0.12 ± 0.03
1hr of Feeding following a Period of Food Deprivation		0.08 ± 0.08	0.11 ± 0.06
24hrs of Feeding Following a Period of Food Deprivation		0.12 ± 0.03	0.12 ± 0.04
Treatment Days	17 - 20	0.11 ± 0.02	0.12 ± 0.02
Treatment Days	20 - 25	0.09 ± 0.02	0.11 ± 0.03
Post-treatment Days	0 - 5	0.1 ± 0.02	0.12 ± 0.02

TABLE XIV

Means (±SDs) of ratios of food spilled to food bitten off in the process of feeding over various periods by rats chronically treated with a moderately high dose of haloperidol (1mg/kg/day for 25 days) and by saline-treated controls.

* $p < 0.05$

Mann-Whitney U test, two-tailed.

6:3(A)(iii) FOOD INTAKE

Food intake, computed as the difference between amount of food missing from the food-hopper and amount spilled, was not significantly different (Mann-Whitney U test) between the two groups prior to the commencement of pharmacological treatment. There was also not a significant difference between the two groups in food intake in the early treatment days as follows: days 0-5 and 5-10. However, food intake was reduced in the experimental group by the 15th day of treatment. Thus food intake was ~~just~~ significantly less in the experimental group than in the control group between the 10th and 15th days of treatment ($p<0.05$, Mann-Whitney U test, one-tailed). Thereafter the difference was accentuated for the remaining ten days of treatment, and appeared to be sharpened even further during the five days immediately following the end of the treatment phase. The difference was significant at the 0.02 level (Mann-Whitney U test, one-tailed) in respect of: (a) food eaten in 24hrs following food deprivation, (b) food eaten between the 17th and 20th days of treatment, and (c) food eaten during the next five days, that is, until a day after the cessation of treatment. The difference between the two groups of ss in the amount of food eaten from the first until the fifth post-treatment day was significant at the 0.01 level (Mann-Whitney U test, one-tailed). Food intake in the first hour of feeding after 24hrs of food deprivation was also less in the haloperidol-treated group than in the saline-treated controls at a highly significant level ($p=0.001$, Mann-Whitney U test, one-tailed). Table XV shows the mean values (in grams) of food actually eaten in the experimental and control groups.

6:3(A)(iv)/

6:3(A)(iv) FAECES

The production of faeces, as determined in terms of the ratio of amount of faeces passed to amount of food actually eaten, was not significantly different between the experimental and control groups of ss in the pre-treatment phase of the study. Haloperidol treatment did not seem to have any observable effect on faeces production; and in the post-treatment phase there was still not a significant difference between the two groups of ss in this regard. Test of significance was by the Mann-Whitney U test. Table XVI shows the mean ratios of faeces to food intake in the various stages of the study.

Periods		Experimental Group of ss (N=6)	Control Group of ss (N=6)
Pretreatment Days	5 - 0	118 ± 11 grams	118 ± 15 grams
Treatment Days	0 - 5	104 ± 18	110 ± 16
Treatment Days	5 - 10	124 ± 5	124 ± 8
* Treatment Days	10 - 15	116 ± 9	128 ± 9
**** 1hr of Feeding following a Period of Food Deprivation		1 ± 1	7 ± 3
** 24hrs of Feeding following a Period of Food Deprivation		29 ± 3	32 ± 2
** Treatment Days	17 - 20	69 ± 7	80 ± 6
** Treatment Days	20 - 25	126 ± 16	147 ± 11
*** Post-treatment Days	0 - 5	128 ± 12	151 ± 13

TABLE XV

Means (±SDs) of food intake by rats chronically treated with a moderately high dose of haloperidol (1mg/kg/day for 25 days) and by saline-treated controls.

* $p < 0.05$

** $p < 0.02$

*** $p = 0.01$

**** $p = 0.001$

Mann-Whitney U test, one-tailed.

Details of the data presented in this table are shown in Appendix C.

Periods		Experimental Group of ss (N=6)	Control Group of ss (N=6)
Pretreatment Days	5 - 0	0.40 ± 0.02	0.39 ± 0.03
Treatment Days	0 - 5	0.44 ± 0.07	0.42 ± 0.08
Treatment Days	5 - 10	0.43 ± 0.04	0.42 ± 0.05
Treatment Days	10 - 15	0.38 ± 0.03	0.38 ± 0.02
Treatment Days	17 - 20	0.37 ± 0.04	0.36 ± 0.03
Treatment Days	20 - 25	0.39 ± 0.03	0.39 ± 0.04
Post-treatment Days	0 - 5	0.37 ± 0.02	0.36 ± 0.03

TABLE XVI

Means (±SDs) of ratios of faeces passed to food actually ingested over various periods by rats chronically treated with a moederately high dose of haloperidol (1mg/kg/day for 25 days) and by saline-treated controls.

The differences between the experimental and control groups are not statistically significant (Mann-Whitney U test).

EXPERIMENT II: FEEDING AND BODY WEIGHT REGULATION DURING AND AFTER CHRONIC TREATMENT WITH A VERY HIGH DOSE OF HALOPERIDOL

6:2(B) MATERIALS AND METHODS

6:2(B)(i) SUBJECTS

The ss comprised 12 male Wistar albino rats weighing between 140g and 155g at the start of the experiment. Throughout the study the ss were housed individually in a reverse daylight room as already described (2:1). Food and water were provided at all times except that they were not available during 1hr of data-collection each day (2:4).

6:2(B)(ii) PROCEDURE

For details of the general procedure employed in the collection of data see 2:4. The present experiment was designed to progress through four successive stages. The first stage, which lasted three days and which may be described as the pretreatment stage, was commenced after an initial disturbance-free environmental orientation period, as described elsewhere (2:1). In this stage, the ss were each given two i.p. injections of 2ml/kg of isotonic saline daily - one at 8.30am and the other at 4.30pm. The saline injections were given twice daily in order to control for the possible effects of such a frequency of treatment (twice daily), which was intended for the second, and critical, stage of the experiment.

In the second stage, which like the first comprised three data-gathering sessions carried out at regular times on three consecutive days, six experimental ss were treated with haloperidol at a dose of 5mg/kg (in isotonic saline, 2ml/kg) twice daily (after Ungerstedt and Ljungberg, 1975) while six control ss continued to receive the bare isotonic/

isotonic saline. Thus each experimental s received a daily haloperidol dose of 10mg/kg whereas the control ss continued to receive only the saline vehicle solutions (4ml/kg daily).

The experimental operations of the third stage closely resembled those of the pretreatment stage in that they comprised three normal data-gathering sessions (see 2:4) carried out regularly on three consecutive days on which all ss received a morning- and an evening-injection of isotonic saline (2ml/kg) at a time).

The chief aim of the fourth stage of the experiment was to ascertain whether supersensitivity of DA receptors, which develops as a result of chronic treatment with haloperidol or other neuroleptics, and is reflected in the enhancement of behavioural sensitivity to DA receptor stimulation (Fjalland and Moller-Nielson, 1974; Gianotsus, Drawbaugh, Hynes and Lal, 1974; Tarsy and Baldessarini, 1973; Ungerstedt and Ljungberg, 1975; Von Voigtlander, 1974), would manifest in changes in ingestive behaviour. It is known that rats rendered aphagic and adipsic by bilateral nigrostriatal damage resume feeding and drinking when administered apomorphine at the dose of 0.1mg/kg (Ungerstedt, and Marshall, 1975). It seemed reasonable, therefore, to expect that this low dose of apomorphine would reverse the depression of food intake which accompanies chronic haloperidol treatment (6:3(B)(iii)).

A high dose of apomorphine (1.0mg/kg) was also used in the experiment to check on the question of haloperidol-induced supersensitivity of DA receptors from the point of view of the disruption of ingestive behaviour. It was predicted that haloperidol ss would perform more stereotyped behaviour than controls following treatment with this relatively high dose of apomorphine and would as a result ingest less food. Because

apomorphine is a short-acting drug it was decided to measure its effects on ingestive behaviour just 1½hrs after its administration.

The operations of this stage were carried out on the seventh (A), eighth (B) and tenth (C) days after haloperidol treatment was commenced, as follows:-

A - All ss received isotonic saline (1ml/kg) and were immediately returned to their cages, which had been prepared in the usual way (see 2:4). Water and food intake and food spillage were measured 1½hrs later on.

B - All ss received a low dose of apomorphine (0.1mg/kg in isotonic saline, 1ml/kg), and were immediately returned to their cages, which had been prepared as usual (see 2:4). Water and food intake and food spillage were measured 1½hrs later on.

C - All ss received a moderately high dose of apomorphine (1.0mg/kg in isotonic saline 1ml/kg), and were immediately returned to their cages which had been prepared in the usual way (see 2:4). Water and food intake and food spillage were measured 1½hrs later on.

6:3(B) RESULTS

In the treatment schedule employing a total daily dose of 10mg/kg of haloperidol for three days the data from the experimental and control groups of ss are compared mainly for periods of three days. The effects of apomorphine administration after the cessation of haloperidol treatment/

treatment are, however, estimated from records taken 1½hrs after a dose of apomorphine or isotonic saline, and the data relevant to the determination of any such effects are analysed and presented as comparisons of 1½hr-long observations in the two subject groups.

In the analysis of the data from the present experiment the first day of haloperidol treatment is the 24hr period immediately following the first haloperidol dose, and the last day of treatment means the 24hr period following the last haloperidol dose.

6:3(B)(i) BODY WEIGHT

Increases in body weight achieved in the three days just preceding the commencement of differential pharmacological treatment were not significantly different (Mann-Whitney U test) between the experimental and control groups of ss. However, in the three days of haloperidol treatment the experimental group gained significantly less weight than the saline-treated control group ($p=0.002$, Mann-Whitney U test, two-tailed). The haloperidol-treated ss quickly returned to normal in the rate of body weight increase when treatment was discontinued; thus the amount of weight gained by this group in the three days following the last day of haloperidol treatment was not significantly different from the weight increase observed in the control group in the same period (Mann-Whitney U test). Table XVII shows the weight increases observed in the two groups in the pre-treatment, treatment and post-treatment 3-day stages of the study. The mean patterns of body weight in the two groups over the period of the experiment are depicted in Figure 21.

Periods		Experimental Group of ss (N=6)	Control Group of ss (N=6)
Pretreatment Days	3 - 0	12 ± 3 grams	14 ± 4 grams
*Treatment Days	0 - 3	3 ± 2	16 ± 2
Post-treatment Days	0 - 3	14 ± 2	16 ± 3

TABLE XVII

Means (±SDs) of weight gained over various periods by rats chronically treated with a very high dose of haloperidol (10/kg/day for 3 days) and by saline-treated controls.

*p = 0.002

Mann-Whitney U test, two-tailed.

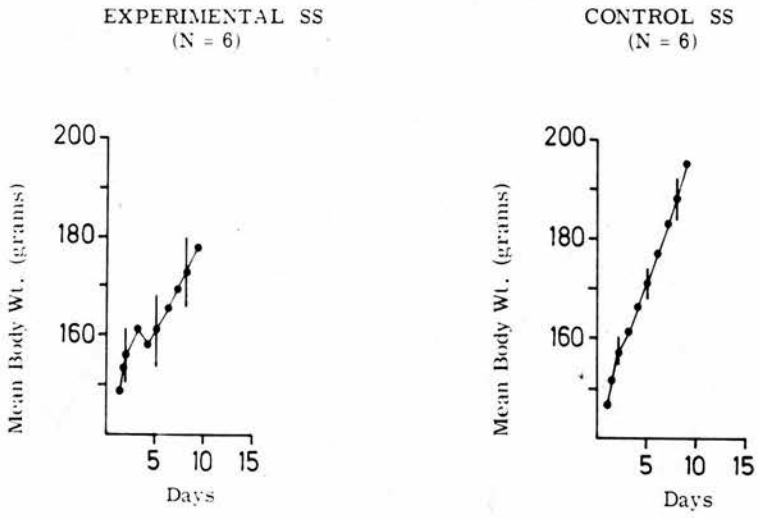


FIGURE 21:

Mean body weights displayed from day to day by rats chronically treated with a very high dose of haloperidol (10mg/kg/day for 3 days) and by saline-treated controls. The two groups were similar in mean body weights prior to the introduction of haloperidol treatment into the study. However, following the first day of treatment the haloperidol-treated group suffered a marked loss of weight and remained under-weight, relative to the control group, for the duration of the study.

The bars represent the SDs at the points in time indicated.

The SDs were computed for each day of the study; for the sake of clarity, however, only a few are shown in the graph.

6:3(B)(ii) FOOD SPILLAGE

Food spillage, computed as the ratio of amount of food spilled to amount removed from the food-hopper, appears to have been reduced by haloperidol treatment. Thus, although food spillage was not significantly different between the experimental and control groups prior to the first day of haloperidol treatment, it was significantly less in the experimental group in the 3 days of treatment ($p<0.01$, Mann-Whitney U test, two-tailed). ~~and also in the 3 days immediately following the last day of treatment ($p<0.05$, Mann-Whitney U test, one-tailed).~~

However, the effect of haloperidol treatment on food spillage appears to have worn off by the fourth post-treatment day since food spillage (computed as described above) was not significantly different between the two groups in 1½hr of feeding following the intraperitoneal (i.p.) administration of isotonic saline on that day (Mann-Whitney U test). Furthermore, there was not a significant difference between the two groups in food spillage in 1½hr of feeding following the i.p. injection of 0.1mg/kg of apomorphine on the fifth post-treatment day or 1.0mg/kg of the same drug 48hrs later on. Table XVIII shows the mean ratios of food spilled to food missing from the food-hopper in the experimental and control groups in the various stages of the study.

6:3(B)(iii) FOOD INTAKE

Like body weight increase and food spillage, food intake (computed as the difference between food removed from the food-hopper in the process of feeding and food spilled in the same process) was not significantly/

significantly different between the two groups prior to the introduction of haloperidol treatment in the experimental group. From this first day of haloperidol treatment, the experimental ss displayed a clear drop in food intake; and food intake remained relatively low until three days after the last day of haloperidol administration. Thus food intake was significantly lower in the experimental than in the control group in the 3 days of haloperidol treatment ($p \leq 0.001$, Mann-Whitney U test, one-tailed) and in the 3 days immediately following the last day of haloperidol treatment ($p < 0.03$, Mann-Whitney U test, one-tailed). There was, however, not a significant difference between the two groups in food intake in 1½hrs following the i.p. administration of isotonic saline on the fourth day after haloperidol treatment was discontinued, or following the administration of apomorphine the next day (0.1mg/kg, i.p.) or two days later on (1.0mg/kg, i.p.). Test of significance was by the Mann-Whitney U test. Table XIX shows the mean food intake by the experimental and control groups in the various stages of the study.

6:3(B)(iv) WATER INTAKE

Water intake also appears to have been depressed by haloperidol treatment in a way similar to the depression of food intake. Thus although the amount of water (in millilitres) missing from the water-bottle was not significantly different (Mann-Whitney U test) between the two groups in the 3 days preceding the introduction of haloperidol treatment into the study, the amount was significantly less for the experimental (haloperidol-treated) group in the 3 days of treatment ($p \leq 0.01$, Mann-Whitney U test, one-tailed) and in the 3 days following the/

the last day of haloperidol treatment ($p<0.05$ Mann-Whitney U test, one-tailed). Like food intake and food spillage, water consumption appears to have returned to normal levels by the fourth day after the end of the haloperidol phase, as there was not a significant difference between the experimental group and the saline-treated controls in the amount of water missing from the water-bottle in 1½hrs following the administration of isotonic saline on that day (Mann-Whitney U test). Moreover, there was not a significant difference between the two groups in the amount of water missing from the water-bottle in 1½hrs following the administration of 0.1mg/kg of apomorphine on the fifth day after the haloperidol phase or of 1.0mg/kg of apomorphine two days later on (Mann-Whitney U test).

Table XX shows the means of water intake by the experimental and control groups throughout the study.

6:3(B)(v) FAECES

The ratio of faeces produced to food ingested was not significantly different between the experimental and control groups of ss before haloperidol treatment was introduced into the study, during the three days of haloperidol administration to the experimental ss or in the three days following the end of the haloperidol treatment (Mann-Whitney U test). Table XXI shows the mean ratios of faeces passed to food intake in the two groups of ss in the pre-treatment, treatment and immediate post-treatment 3-day periods.

Periods		Experimental Group of SS (N=6)	Control Group of SS (N=6)
Pretreatment Days	3 - 0	0.11 ± 0.04	0.13 ± 0.03
** Treatment Days	0 - 3	0.08 ± 0.02	0.13 ± 0.02
Post-treatment Days	0 - 3	0.08 ± 0.03	0.11 ± 0.02
1½hr of Feeding following Saline Administration (1ml/1g)		0.06 ± 0.05	0.08 ± 0.04
1½hr of Feeding following Apomorphine Administration (0.1mg/kg)		0.09 ± 0.02	0.14 ± 0.09
1½hr of Feeding following Apomorphine Administration (1.0mg/kg)		0.09 ± 0.05	0.11 ± 0.04

TABLE XVIII

Means (±SDs) of ratios of food spilled to food bitten off in the process of feeding over various periods by rats chronically treated with a very high dose of haloperidol (10mg/kg/day for 3 days) and by saline-treated controls.

**$p < 0.01$

Mann-Whitney U test, two-tailed.

Periods		Experimental Group of SS (N=6)	Control Group of SS (N=6)
Pretreatment Days	3 - 0	63 ± 5 grams	61 ± 2 grams
** Treatment Days	0 - 3	55 ± 2	68 ± 4
Post-treatment Days	0 - 3	65 ± 3	70 ± 4
1½hr of Feeding following Saline Administration (1ml/1g)		3 ± 1	4 ± 2
1½hr of Feeding following Apomorphine Administration (0.1mg/kg)		3 ± 2	3 ± 1
1½hr of Feeding following Apomorphine Administration (1.0mg/kg)		2 ± 1	3 ± 1

TABLE XIX

Means (±SDs) of food intake by rats chronically treated with a very high dose of haloperidol (10mg/kg/day for 3 days) and by saline-treated controls.

*$p < 0.03$

**$p = 0.001$

Mann-Whitney U test, one-tailed.

Details of the data presented in this table are given in Appendix D.

Periods		Experimental Group of SS (N=6)	Control Group of SS (N=6)
Pretreatment Days	3 - 0	82 ± 8ml	85 ± 5ml
** Treatment Days	0 - 3	76 ± 12	94 ± 5
* Post-treatment Days	0 - 3	86 ± 11	90 ± 6
1½hr of Feeding following Saline Administration (1ml/kg)		6 ± 1	7 ± 2
1½hr of Feeding following Apomorphine Administration (0.1mg/kg)		9 ± 1	10 ± 6
1hr of Feeding following Apomorphine Administration (1.0mg/kg)		3 ± 0	4 ± 1

TABLE XX

Means (±SDs) of water intake by rats chronically treated with a very high dose of haloperidol (10mg/kg/day for 3 days) and by saline-treated controls.

*$p < 0.05$

**$p = 0.01$

Mann-Whitney U test, one-tailed.

For details of the data presented in this table see Appendix E.

Periods		Experimental Group of SS (N=6)	Control Group of SS (N=6)
Pretreatment Days	3 - 0	0.31 ± 0.01	0.30 ± 0.02
Treatment Days	0 - 3	0.32 ± 0.02	0.31 ± 0.02
Post-treatment Days	0 - 3	0.35 ± 0.03	0.32 ± 0.02

TABLE XXI

Means (±SDs) of ratios of faeces passed to food actually ingested over various periods by rats chronically treated with a very high dose of haloperidol (10mg/kg/day for 3 days) and by saline-treated controls.

The differences between the experimental and control groups are not statistically significant. (Mann-Whitney U test).

DISCUSSION

6:4(i) EFFECTS OF CHRONIC HALOPERIDOL TREATMENT ON FOOD AND WATER INTAKE

As tables XIX and XX show haloperidol treatment depressed food and water intakes in the acute phase when the heavy dose of 10mg/kg/day was administered and food and water intakes remained below control levels throughout the three days of treatment and the three days of immediate post-treatment observation. Also from Table XV it can be seen that chronic treatment with the dose of 1mg/kg/day led to a marked reduction in food intake by the 20th day of treatment, and the reduction was still evident for five days after treatment was discontinued on the 30th day of the particular treatment.

An explanation for the observed deficits in ingestive behaviour is not readily available, but it should perhaps be mentioned that at certain stages of the studies the haloperidol-treated groups of ss appeared lethargic each morning and were thus easier to weigh than controls. The sedation observed in these animals was not due to an acute effect of treatment since the ss were injected after their body weights were measured (see 2:4). What is interesting about the appearance of "chronic" lethargy in the haloperidol-treated groups of ss in the two experiments is that it corresponded roughly to the initial drop in food intake. Although no quantitative measurement of activity was undertaken in the experiments, it seems that the observed reductions in food and water intakes were related to reduced calorie needs associated with a lowering of general activity levels due to haloperidol treatment; the ingestive deficits may also be related to a general reduction in the ability to move about and carry out active functions, including eating and drinking.

6:4(ii) CHRONIC HALOPERIDOL TREATMENT AND BODY WEIGHT REGULATION

From Figures20 and 21 it is evident that haloperidol treatment can have a depressant effect on body weight. Thus the group of ss treated with the heavy daily dose of 10mg/kg lost weight markedly in the first 24hrs of treatment and the group receiving a daily dose of 1mg/kg was exhibiting a clear deficit in the pattern of body-weight increase by the 20th day of treatment. However, it is interesting to note that the drop in body weight observed following the first dose of 10mg/kg was not sustained, as the ss were gaining weight normally by the second and third days of treatment and throughout the three days of immediate post-treatment observation (Figure 21; Table XVII). This observation is not consistent with the sustained reductions in food and water intake throughout the treatment and immediate post-treatment observation periods (Tables XIX and XX). Similarly, it should be noted that whereas depression of food intake was evident by the 15th day of treatment with the daily dose of 1.0mg/kg (Table XV) body weight was not depressed until the 20th day of treatment (Table XIII and Figure 20). Thus chronic treatment with haloperidol appears to have a facilitatory effect, up to a point, on body weight gain per unit amount of food ingested. In other words, animals treated with haloperidol over a period of several days tend to maintain their body weights on a relatively lower amount of food intake once the acute weight-depressant effect of a very high initial dose is over (Figure 21) or until the cumulative effect of a low daily dose begins to disrupt the normal pattern of body weight regulation (Figure 20).

The precise mode of action of haloperidol in the regulation of the body/

body weight of animals subjected to prolonged treatment is not clear. However, the apparently facilitatory effect on body weight may be related to a lowering of the general activity level of treated animals which means that less of the ingested food is used up in the production of energy. It may, on the other hand, be that the observed facilitation of body weight increase represents a direct action in the regulation of body weight. Further work is necessary before we can be sure just how chronic haloperidol treatment exerts its rather curious influence on body weight regulation. A lesion study reported later in this thesis (Chapter 7) was designed partly to unravel some of this mystery.

6:4(iii) EFFECT OF CHRONIC HALOPERIDOL TREATMENT ON FOOD SPILLAGE: CLINICAL IMPLICATIONS

A most interesting observation in the present experiments is that chronic haloperidol treatment, at the two doses used, reduced food spillage as computed in terms of the ratio of quantity spilled to quantity bitten off in the process of feeding. It may be recalled (6:1(ii)) that the chief objective of the present studies was to ascertain whether the effects of nigrostriatal pathway damage on feeding and body weight (see Figure 6 and Tables, I, IV and V) could be produced through the pharmacological blockade of the DA receptors in the brain. Thus the author's prediction that chronic haloperidol treatment would, like unilateral nigrostriatal pathway damage, increase the rate of food spillage has been proved wrong by the results of the experiments.

In a previous study (Chapter 3), it was demonstrated that increased food spillage could reflect sensorimotor dysfunction, and does in animals sustaining a unilateral destruction of the nigrostriatal DA system. It has been proposed also that sensorimotor function is controlled/

controlled through a neural transmission network of which the nigro-striatal DA system is part (3:4(ii)). Interrupting this network at any point would lead to sensorimotor dysfunction. The results of the present experiments have shown that haloperidol treatment does not enhance food spillage. It may be concluded, therefore, that haloperidol administration does not really interrupt the nigro-striatal pathway.

Reduction of food spillage by haloperidol may be related to this drug's therapeutic action. It is strongly suggested by results from several investigations that certain forms of psychoses - e.g. schizophrenia, which is treated with haloperidol and other neuroleptic agents - are associated with an abnormally high level of activity at central DA receptor sites (Angrist, Sathananthan and Gershon, 1973; Angrist, Shopsin and Gershon, 1971; Ellinwood, Sudilovsky and Nelson, 1972; Randrup and Munkvad, 1970). If this view is correct, then at least part of the antipsychotic action of haloperidol may well be exerted through the reduction of "noise" in central dopaminergic synanses. In this regard it is interesting to note that amphetamine and apomorphine, which are known to enhance activity in central dopaminergic synapses, produce stereotyped behaviour, and that this effect is antagonised by haloperidol and other DA receptor blocking agents (Ernst, 1967; Fuxe, and Ungerstedt, 1970; Ungerstedt, Butcher, Butcher, Anden and Fuxe, 1969). The reduction of food spillage by haloperidol treatment in the present experiments suggeststhat the level of noise in the central dopaminergic synapses of normal animals is a bit too high for maximum efficiency in certain behavioural functions, notably sensorimotor control of food spillage. It would appear that in these experiments haloperidol reduced/

reduced the noise level in a way similar to the drug's antagonism of amphetamine- or apomorphine-induced stereotypy in order to produce the kind of enhanced efficiency which was reflected in reduced food spillage.

CHAPTER 7

BEHAVIOURAL EFFECTS OF UNILATERAL KAINATE LESION OF THE STRIATUM

7:1 INTRODUCTION

7:1(i) SOME BEHAVIOURAL EFFECTS OF 6-HYDROXYDOPAMINE-INDUCED LESION OF THE NIGROSTRIATAL DOPAMINE SYSTEM

The results of a previous experiment (see 4:2(A) and 4:3(A)) show that microinjection of 6-OHDA into the MFB on one side of the brain produced certain clearly demonstrable behavioural effects in the rat. Thus nine rats trained to push the lever for food reward in an operant behaviour box and then given a 6-OHDA microinjection into the MFB on the side contralateral to the preferred forepaw displayed a definite shift in forepaw preferences when tested a week after surgery, and eight of them pressed the lever with virtually only the ipsilateral forepaw when tested seven weeks later on. Rats with an ipsilateral 6-OHDA lesion of the MFB exhibited an accentuation of the preoperative forepaw preference. Rats with a control surgical treatment did not exhibit any alteration of their behaviour when tested one week or eight weeks after surgery.

At the one week postoperative test the rate of lever-pressing was significantly depressed in rats with a contralateral MFB lesion. Rats sustaining an ipsilateral MFB lesion also showed a certain amount of reduction in rates of lever-pressing. Control ss showed a small increase in rates, on the other hand. In all ss (experimental and control ss alike) the greater number of abortive presses were made with the forepaw used for most of the effective presses; this was the case after as well as before surgery. Finally, although unilateral MFB damage had no consistent effect on lever preference in the operant behaviour/

behaviour box design used, all the lesioned ss exhibited enhanced spontaneous rotation, which was exclusively ipsiversive.

In another set of experiments (see 3:2 and 3:3) rats with a unilateral 6-OHDA destruction of the nigrostriatal DA pathway displayed a chronic reduction of food intake (Table IV) and body weight (Figure 6), coupled with a dramatic enhancement of food spillage (Table V). In line with findings presented elsewhere (Figure 9), such rats pressed the lever with only the forepaw on the lesion side (Figure 7a(i)) and displayed an exclusive preference for the ipsilateral direction of rotation (Figure 7d(i)) when trained 12wks after surgery to operate levers for food reward on a continuous reinforcement schedule in a Skinner box. The control group of ss, on the other hand, resumed normal feeding and body weight patterns within 48hrs after surgery, and, when observed in the Skinner box 12wks later on, exhibited random forepaw use and rotated normally.

7:1(ii) LIMITED SPECIFICITY OF ACTION OF 6-HYDROXYDOPAMINE

The biochemical assay of striatal catecholamine concentrations in animals used in the 6-OHDA experiments showed a substantial depletion of DA in the denervated striatum of the lesioned ss; however, the lesioning technique employed in that study caused also a reduction of striatal NE, and a further catecholamine assay revealed similar reductions in extrastriatal forebrain levels of DA and NE (Tables VIII and IX). These assay results precipitated an interpretational problem since the observed behavioural and other effects of the lesion might conceivably be due to the disruption of catecholamine systems supplying extrastriatal forebrain/

forebrain regions. It became necessary, therefore, to use a lesioning technique that could spare at least some of the catecholamine systems amenable to MFB injection of 6-OHDA and at the same time disrupt the nigrostriatal DA system. The experiments reported in the present chapter were designed primarily to deal with the interpretational problem just mentioned.

KAINIC ACID AS AN EXPERIMENTAL TOOL

Excitatory amino acids, for example glutamic acid, are known to exert their depolarization action on the dendrites and soma of a neuron, axons being unresponsive (Curtis, Duggan, Felix, Johnston, Trebecis and Watkins, 1972; Zieglgansberger and Puil, 1975). Following the subcutaneous administration of monosodium glutamate to immature mice, neurons with cell bodies in the arcuate nucleus of the hypothalamus degenerate, whereas axons which terminate in or pass through this area appear to remain intact (Perez and Olney, 1972; Perez, Olney, Frolichstein, Martin and Cannon, 1976). The arcuate nucleus is known to accumulate high concentrations of glutamate (Perez and Olney, 1972). Certain findings have suggested that the neurotoxic effects of glutamic acid are the result of excessive neuroexcitation (see Olney, Ho and Rhee, 1972).

Kainic acid, an analogue of glutamate, is a more potent neuroexcitant than glutamate (Buu, Puil, and Van Gelder, 1976; McLennan, 1975). Schwarcz and Coyle (1977) have explored the neurochemical characteristics of intrastriatal microinjection of kainic acid. Injecting 2.5ug of kainic acid into the striatum, they obtained a 70% reduction/

reduction of choline acetyltransferase (CAT) and acetylcholine (ACh) and a similar reduction of glutamic acid decarboxylase (GAD) and gamma-aminobutyric acid (GABA), whereas the level of DA in the striatum was unaffected. There was almost a complete loss of neurons intrinsic to the injected striatum; but fibres of the internal capsule were intact and there was no evidence of non-specific tissue necrosis. On the basis of these findings the authors proposed that kainic acid appears to be a useful tool for selectively lesioning neuronal perikarya in restricted regions of the brain. Such an experimental tool seemed inviting as an aid in limiting the interpretational possibilities encountered in the 6-OHDA studies presented in this thesis (see 3:3(iii); 4:3(A)(ii); 4:3(C)(ii); and 4:4(viii)).

The microinjection of 6-OHDA into the MFB disrupts the nigrostriatal DA system presynaptically. With particular reference to the main focus of the present thesis (the nigrostriatal DA system) the chief limitation of that 6-OHDA procedure is that it leads to the disruption of not only the nigrostriatal DA system but also other catecholamine systems supplying the forebrain regions via the MFB. It was, therefore, decided to "attack" the nigrostriatal system post-synaptically by ablating, with the help of kainic acid, the neuronal perikarya intrinsic to the striatum and to observe the effects of such a lesion on behaviour. Since the neurotoxic action of intrastriatally administered kainic acid would be restricted to striatal intrinsic neuronal perikarya (Coyle and Schwarcz, 1976; Schwarcz and Coyle, 1977), DA and NE supplies to extrastriatal forebrain areas should be intact; and if the behavioural changes observed after MFB microinjection of 6-OHDA/

6-OHDA are reproduced through kainic acid lesion of the striatum, such changes are so much the more likely to be due to the disruption of the nigrostriatal dopaminergic mechanism, although the extent of involvement of the NE fibres supplying the striatum via the MFB remains unknown.

EXPERIMENT I: INGESTIVE BEHAVIOUR AND BODY WEIGHT REGULATION FOLLOWING A UNILATERAL KAINATE-INDUCED LESION OF THE STRIATUM

7:2(A) MATERIALS AND METHODS

7:2(A)(i) SUBJECTS

The ss were 13 male Wistar albino rats. Seven of these served as experimental ss, whereas the other six constituted the control group. All the ss weighed between 170g and 205g at the time of surgery. Throughout the study the ss were housed in individual cages in a reverse daylight room as previously described (2:1). Food and water were provided at all times except that (a) neither food nor water was available during the 1hr of data-collection each day (2:4) and (b) food or water was selectively withdrawn for 24hrs when responses and reactions to its deprivation were to be investigated.

7:2(A)(ii) COLLECTION OF DATA RELATING TO INGESTIVE BEHAVIOUR AND BODY WEIGHT REGULATION

The general procedure for data-collection in respect of ingestive behaviour and body weight is the same as previously described (2:4). After 1wk of routine environmental orientation (2:1) data-collection was commenced in the usual way (2:4). The daily data-gathering sessions included measurements of water intake, food intake, food spillage, and body weight. Owing to the tendency of spilled water

to/

to be lost, notably through evaporation, it was not possible to separate water actually ingested from water spilled in the process of drinking.

Seven regular daily sessions of data-gathering measurements were carried out in the preoperative stage of the experiment. The ss underwent surgery immediately after the seventh of these sessions.

The first of the daily sessions of data-gathering measurements in the postoperative stage took place 44hrs after surgery, and ushered in a fortnight of regular daily sessions. After the 14th post-operative data-gathering session the ss were deprived of food for 24hrs. Just before food was restored the body weights of the ss were measured to determine the amount of weight lost over the period of food deprivation. Twenty-four hours later a full session of data-gathering measurements was carried out. Thereafter the ss were not disturbed for five days. Then the ss were deprived of water for 24hrs. Before the restoration of water the body weights of the ss were measured to determine the amount of weight loss sustained over the period of water deprivation. A full data-gathering session carried out 24hrs later on constituted the last of such sessions in the experiment.

7:2(A)(iii) SURGERY

The ss were anaesthetized with a mixture of air and fluothane and operated upon by a procedure already described (2:5; 2:7 and 2:8). Each experimental s received 1.5ug of kainic acid in 0.3ul of isotonic saline. Control ss received the bare saline vehicle (0.3ul each). Each injection was administered over a period of seven minutes; and the injection target was the left striatum for all ss.

7:2(A)(iv) DISSECTION

All the ss used in this experiment were sacrificed two weeks after the final data-gathering session carried out in respect of ingestive behaviour and body weight (7:2(A)(ii)). The animals were killed by decapitation after being stunned with a blow. Nigral, striatal and limbic samples were dissected out from each hemisphere of every s for the estimation of certain neurochemical effects of surgery (see 7:2(A)(v)).

An additional specimen was obtained for use in the histological estimation of damage to extra-striatal structures due to surgery. A detailed description of the dissection procedure is given elsewhere (2:9).

7:2(A)(v) BIOCHEMISTRY

Immediately after each striatal sample was dissected out and before it was stored in liquid nitrogen (2:10) it was crushed up and divided into two parts for separate biochemical assays of CAT and GAD activities. The nigral sample from each side of the brain was used for GAD assay only, unfortunately. CAT was determined by a modification of the method of Fonnum (1975), and GAD was assayed using a combination of the methods of Urquhart et al., (1975) and Drummond and Phillips (1974). The limbic forebrain sample from each hemisphere was used for the determination of DA and NE concentrations according to the radio-enzymatic method of Coyle and Henry (1973) and Palkovitz et al., (1973). Details of the biochemical assay procedures are given in Chapter 2 (2:12; 2:13, and 2:14).

7:2(A)(vi) HISTOLOGY

Following dissection the tissue specimen for histological examination/

examination was mounted on a disc of cork and frozen quickly with the help of solid carbon dioxide. 20u sections were cut with the help of a cryostat, and one in every five sections was picked. The sections were stained with luxol fast blue (for fibres) and cresyl fast violet (for cell-bodies) according to a modification of the method of Kluver and Barrera (1951), as previously described (2:11). The sections were mounted with DPX and viewed under a light microscope.

7:3(A) RESULTS

7:3(A)(i) BIOCHEMICAL ASSAY RESULTS.

All the ss showed a substantial drop in the activities of CAT and GAD in the lesioned striatum. At the striatal level some ss suffered a larger reduction in CAT than GAD activity, whereas the drop in GAD activity was greater in some other ss. Taken together, though, the combined activities of CAT and GAD in the lesioned striatum were reduced by more than 50% in all the ss except one which suffered only a 49% drop.

GAD activity in the substantia nigra on the lesion side was reduced to some extent in all ss except the one which also escaped a huge drop in combined striatal CAT and GAD activities as reported in the previous paragraph.

Limbic forebrain DA was not substantially reduced on the lesion side. In fact, two ss had a slightly higher DA content on the side of lesion; and one other s had only a 5% loss; these did not include the animal mentioned in the previous paragraphs as sustaining a relatively small degree of drop in CAT and GAD activities.

NE content of the limbic forebrain was not consistently reduced on the/

the side of lesion. Thus, for example, one s actually had a higher limbic forebrain level of NE on the side of lesion and two other ss lost 6% and 8% of this catecholamine respectively.

Table XXII presents the biochemical assay results in terms of percent reduction on the lesion side.

There was no significant correlation between the intensity of lesion-induced alterations in ingestive behaviour and body weight regulation and the severity of damage to any one neurochemical system in any of the brain regions sampled (Kendall's tau).

7:3(A)(ii) HISTOLOGICAL RESULTS

In 6 out of the 7 ss used in the present study there was no damage to such extrastriatal structures as were observable in the sections prepared for histological examination (see 7:2(A)(vi)). Thus the pallidum and the thalamus, for example, appeared undamaged on the lesion side as on the intact side. Figure 22 presents photomicrographs of the pallidum on each side of a typical lesioned s.

However, the seventh animal in the group of ss lesioned for the purposes of the experiment presented a clear disruption of the pallidum on the lesion side. Figure 23 shows the appearance of each pallidum in this s. This s was, of course, not included in the analysis of the behavioural effects of Kainate ablation of striatal intrinsic neuronal perikarya.

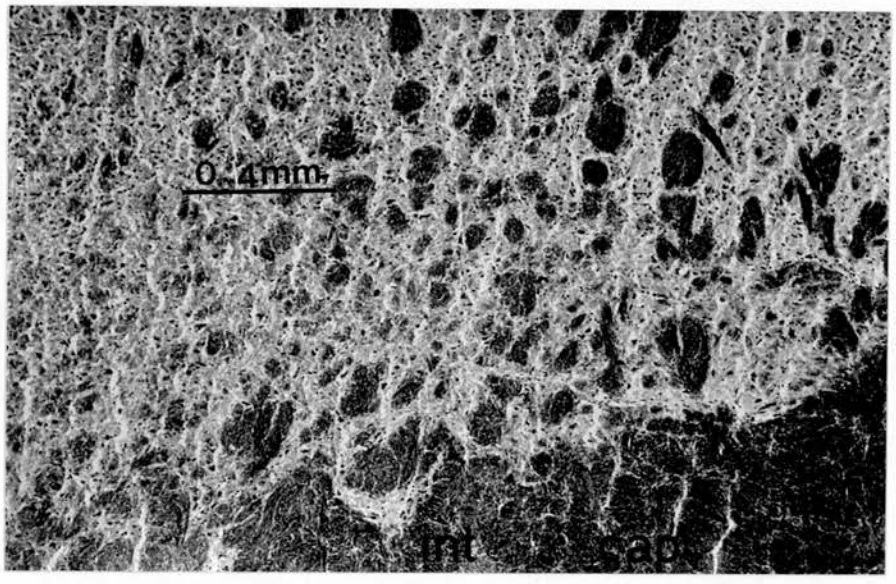
Subject Groups	Subjects	REDUCTIONS ON THE LESION SIDE				
		% Loss in Striatal CAT	% Loss in Striatal GAD	% Loss in Nigral GAD	% Loss in ■"Limbic" DA	% Loss in ■"Limbic" NE
Kainate Lesioned (experimental) Group	A	52	61	27	0	0
	B	55	85	13	12	16
	C	86	100	33	19	32
	D	94	69	59	36	36
	E	92	73	50	0	6
	F	96	100	59	5	18
	*G	69	29	0	33	8
	Mean ±SD	79 ± 20	81 ±16	40 ± 19	12 ±14	18 ± 14
Vehicle-injected (control) Group	A	0	0	0	13	22
	B	0	0	37	3	14
	C	0	0	0	40	9
	D	0	0	0	0	0
	E	0	0	0	2	0
	F	0	0	21	21	0
	Mean ±SD	0	0	10 ±16	13 ±15	8 ± 9

TABLE XXII

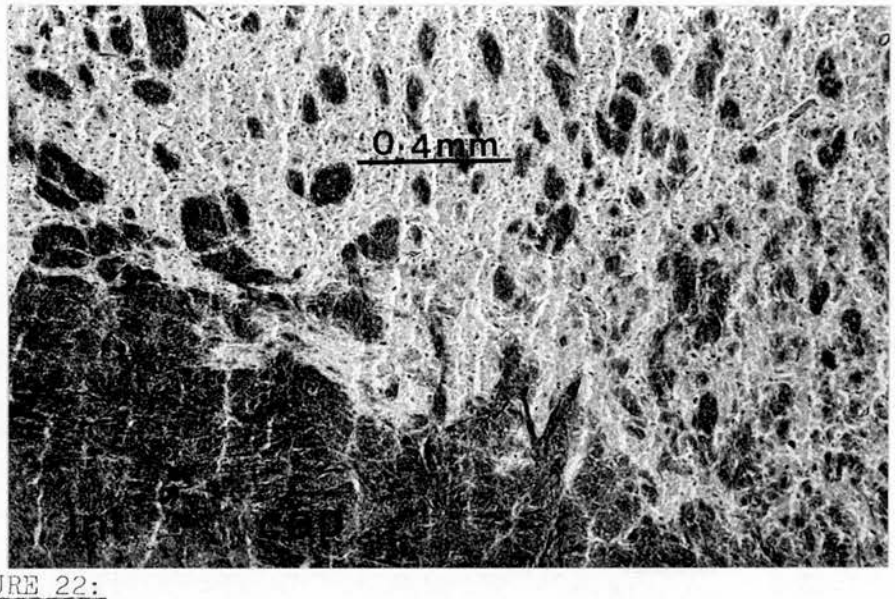
Some neurochemical deficits in the injected hemisphere of rats sustaining a unilateral kainate-induced striatal lesion and of vehicle-injected controls.

* Because this s suffered an extensive pallidal damage on the lesion side it was excluded from all analyses of data relating to the neurochemical and behavioural effects of the lesion.

■ "Limbic" = Limbic forebrain region of the brain (see 2:9).



A



B

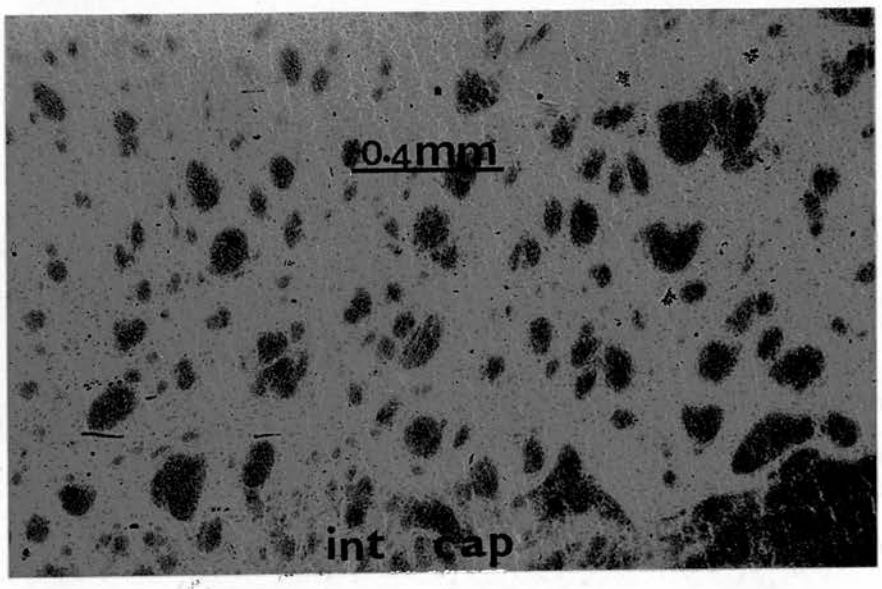
FIGURE 22:

Photomicrographs showing the pallidum on each side of the brain of a typical rat given a unilateral intrastriatal injection of kainic acid without observable damage to extra striatal structures.

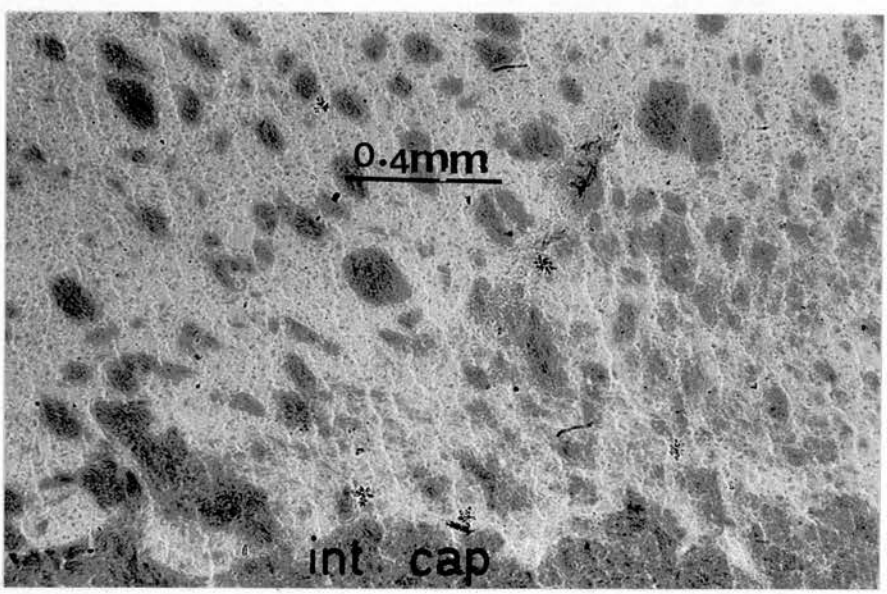
Plate A: pallidum of the lesion side.

Plate B: pallidum of the intact side.

Abbreviation: int. cap., internal capsule



A



B

FIGURE 23:

Photomicrographs showing the pallidum in each hemisphere of a rat sustaining pallidal damage as a result of surgical error in an operation aiming for a unilateral kainate lesion of the striatum.

The difference between Plate A (intact pallidum) and Plate B (damaged pallidum) is marked. This s displayed more pronounced deficits than the other experimental ss in ingestive behaviour (see, for example, Appendix F).

This s (labelled G) was not included in the analysis of data relating to the neurochemical and behavioural effects of unilateral kainate lesion of the striatum.

Abbreviation: int. cap., internal capsule

7:3 (A)(iii) INGESTIVE BEHAVIOUR AND BODY WEIGHT

The results presented in respect of feeding and drinking behaviour and body weight regulation are records from 6 ss which showed no extrastriatal damage in the histological examination of the brain as already described (7:3(A)(ii)). The results are presented mostly for periods of seven days as follows: one week before surgery, first postoperative week, and second postoperative week. The acute effects of surgery, and the animals' reactions and responses to food deprivation and to water deprivation are, however, presented from a single day's record.

Figure 24 depicts mean trends in body weight in the experimental and control groups from day to day throughout the study. The mean trends were similar in the two groups prior to surgery. Following surgery the experimental (kainate-lesioned) group suffered an enormous drop in body weight as compared to the control group, but the weight deficit was not sustained for a long time; in fact, by the 18th postoperative day (i.e. 25th day of study) the experimental group had outstripped the control group in mean body weight. Table XXIII shows the mean increases in body weight displayed by the two groups over periods of seven days just before and for two weeks after surgery. There was not a significant difference between the groups before surgery or in the first postoperative week (Mann-Whitney U test). However, in the second postoperative week the experimental (lesioned) group gained significantly more weight than the control group ($p<0.02$, Mann-Whitney U test, two-tailed).

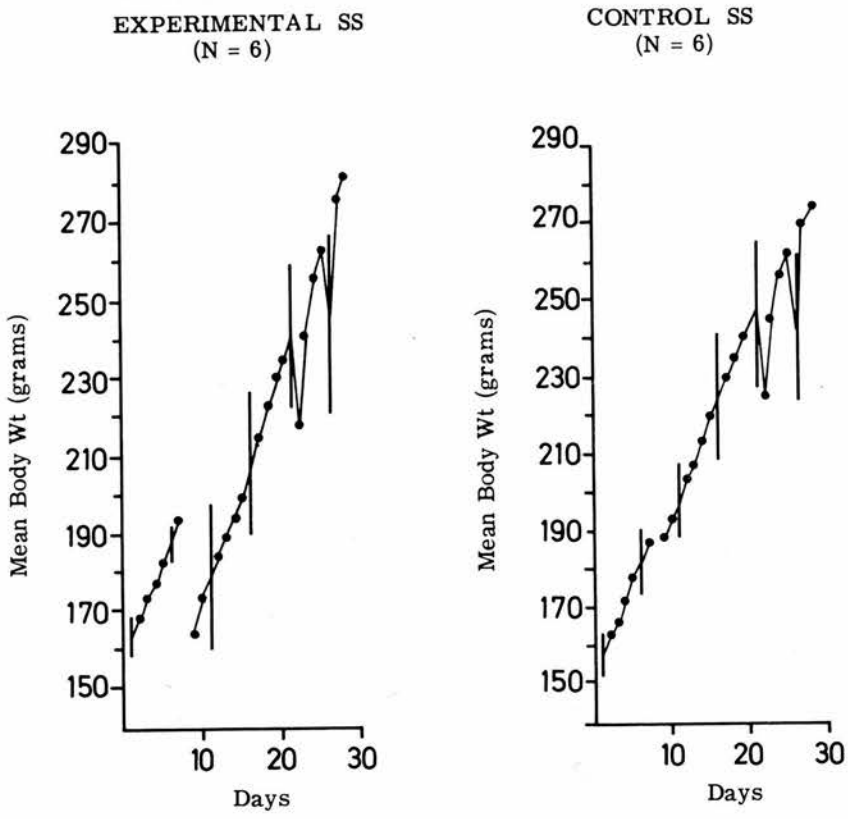


FIGURE 24:

Mean body weights displayed from day to day by rats sustaining a unilateral kainate-induced lesion of the striatum and by controls. The two groups of ss were similar in mean body weights prior to surgery. Following surgery the experimental group suffered a huge loss of weight but recovered within 1wk and actually caught up again with the control group by the 18th postoperative day.

The bars represent the SDs on the days indicated. The SDs were computed for each day of the study; but for the sake of clarity only a few are shown in the graph.

Periods	Experimental Group of ss (N=6)	Control Group of ss (N=6)
Immediate Preoperative Week	30 ± 5 grams	30 ± 6 grams
1st Postoperative Week	36 ± 8	32 ± 7
* 2nd Postoperative Week	41 ± 4	28 ± 7

TABLE XXIII

Means (± SDs) of weight gained by rats with a unilateral kainate-induced striatal lesion and by vehicle-injected controls in the immediate preoperative week, in the 1st postoperative week and in the 2nd postoperative week. 1st postoperative week means that 7-day period immediately succeeding the record taken 44hrs after surgery (see 7:2(A)(ii)).

* p 0.02

Mann-Whitney U test, two-tailed.

The weight increases displayed by the two groups of ss in the immediate postoperative period are presented in Table XXIV. From the table it can be seen that whereas 4 out of 6 control ss had recovered their highest recorded preoperative body weights by 44hrs after surgery, none of the experimental ss had made a similar recovery. The difference between the two groups in weight gained over this period is statistically significant ($p<0.002$, Mann-Whitney U test, two-tailed).

Table XXV shows the body weight changes exhibited by the two groups of ss in the food deprivation and food restoration observation periods. There was no significant difference between the experimental and control groups in the amount of weight lost as a result of 24-hr food deprivation or in weight recovery (i.e. amount of weight gained) 24hrs after the restoration of food. However, the total weight increases observed in the experimental group in the 48hrs taken together were significantly greater than in the control group ($p<0.05$, Mann-Whitney U test, two-tailed).

In Table XXVI are presented the body weight changes recorded in the water deprivation and water restoration observation periods. There was no significant difference between the experimental and control groups in weight lost following 24hrs of water deprivation or weight gained 24hrs after water was restored, or total weight gained in the 48hrs taken together.

The quantity of food spilled by a rat in the process of feeding depends, in the final analysis, upon the quantity removed from the food-hopper for the purpose of consumption. In other words, the more food a particular s chops off, the more it is likely to spill.

Experimental Group of Ss (Kainate-lesioned)		Control Group of Ss (Vehicle-injected)	
Subjects	Wt. Gain	Subjects	Wt. Gain
A	-27.5 grams	A	-2.9 grams
B	-51.1	B	4.5
C	-44.5	C	-1.5
D	-20.4	D	0.8
E	-8.7	E	0.4
F	-24.9	F	4.2
G	-24.9		

TABLE XXIV

Weight gained by rats with a unilateral kainate-induced striatal lesion and by vehicle-injected controls in the 44hr period immediately following surgery.

The difference between the two groups is statistically significant ($p<0.002$, Mann-Whitney U test, two-tailed).

Because subject G of the experimental group turned out to have sustained a pallidal damage (see Figure 23) it was excluded from the analysis of data relating to body weight changes due to kainate lesion of the striatum.

Subject Groups	Subjects	Wt. Lost during Food deprivation	Wt. Gained 24hrs After Food Restoration	Total Wt. Gain (48hrs)*
Experimental (Kainate-lesioned) Group	A	17.6 grams	20.8 grams	3.2 grams
	B	28.6	23.3	-5.3
	C	21.6	20.9	-0.7
	D	25.1	32.0	6.9
	E	27.1	26.7	-0.4
	F	25.3	27.0	1.7
	G	23.0	26.2	3.2
	Mean $\pm$ SD	24 $\pm$ 4	25 $\pm$ 4	1 $\pm$ 4
Control (Vehicle-injected Group	A	20.3	18.3	-2.0
	B	25.1	23.9	-1.2
	C	25.4	18.9	-6.5
	D	24.2	19.2	-5.0
	E	23.2	22.3	-0.9
	F	31.1	29.8	-1.3
	Mean $\pm$ SD	25 $\pm$ 4	22 $\pm$ 4	-3 $\pm$ 2

TABLE XXV

Weight changes observed in rats with a unilateral kainate-induced striatal lesion and in vehicle-injected controls following food deprivation and 24hrs after food restoration.

Because subject G of the experimental group turned out to have sustained a pallidal damage (see Figure 23) it was excluded from the analysis of data relating to body weight changes due to kainate lesion of the striatum.

* $p < 0.05$

Mann-Whitney U test, two-tailed.

Subject Groups	Subjects	Wt. Lost during Water Deprivation	Wt. Gained 24hrs after Water Restoration	Total Wt. Gain (48hrs)
Experimental (kainate-lesioned) Group	A	20.9 grams	30.8 grams	9.9 grams
	B	20.2	34.3	14.1
	C	19.9	23.5	3.6
	D	21.8	34.2	12.4
	E	23.5	32.0	8.5
	F	25.6	35.7	10.1
	G	18.9	27.1	8.2
	Mean $\pm$ SD	22 $\pm$ 2	32 $\pm$ 4	10 $\pm$ 4
Control (Vehicle-injected) Group	A	20.5	25.2	4.7
	B	21.3	23.8	2.5
	C	19.7	32.7	13.0
	D	16.3	25.9	9.6
	E	19.1	27.1	8.0
	F	19.3	33.5	14.2
	Mean $\pm$ SD	19 $\pm$ 2	28 $\pm$ 4	9 $\pm$ 5

TABLE XXVI

Weight changes observed in rats with a unilateral kainate-induced striatal lesion and in vehicle-injected controls following water deprivation and 24hrs after water restoration.

The inter-group differences are not statistically significant (Mann-Whitney U test).

Because subject G of the experimental group turned out to have sustained a pallidal damage (see Figure 23) it was excluded from the analysis of data relating to body weight changes due to kainate lesion of the striatum.

Therefore, food spillage is presented in this experiment, as in similar experiments throughout the thesis, in terms of the ratios of food spilled by the animals to food missing from their food-hoppers. Table XXVII shows the mean ratios for the experimental and control groups in various observation periods. There was no significant difference between the two groups in the 1wk immediately preceding surgery (Mann-Whitney U test). However, the experimental group displayed significantly greater food spillage than the control group in the 1st postoperative week ($p<0.05$, Mann-Whitney U test, one-tailed), in the 2nd post-operative week ($p<0.003$, Mann-Whitney U test, one-tailed), during 24hrs of feeding at the end of the food-deprivation period ($p<0.001$, Mann-Whitney U test, one-tailed) during 24hrs of feeding in the absence of water ($p<0.01$ Mann-Whitney U test, one-tailed) and during 24hrs of feeding at the end of the water-deprivation periods ($p<0.03$ Mann-Whitney U test, one-tailed).

Table XXVIII shows the means of food intake by the experimental and control groups throughout the study. The kainate-lesioned group ingested significantly less food than the control group in the 1st postoperative week ($p=0.002$, Mann-Whitney U test, two-tailed), although the difference between the two groups in the immediate pre-surgery week was not significant. However, there was no significant difference between the two groups in the amount of food ingested in the 2nd postoperative week, during 24hrs of feeding at the end of a period of food-deprivation, during 24hrs of water deprivation or during 24hrs of feeding at the end of a period of water deprivation (Mann-Whitney U test).

Periods	Experimental Groups of ss (N=6)	Control Group of ss (N=6)
Immediate Preoperative Week	0.12 ± 0.03	0.12 ± 0.03
* 1st Postoperative Week	0.2 ± 0.06	0.13 ± 0.03
■ 2nd Postoperative Week	0.21 ± 0.05	0.13 ± 0.03
● 24hrs of Feeding following Food Deprivation	0.26 ± 0.06	0.13 ± 0.03
▼ During 24hrs of Water Deprivation	0.24 ± 0.06	0.14 ± 0.04
** 24hrs of Feeding following Water Deprivation	0.22 ± 0.05	0.14 ± 0.04

TABLE XXVII

Mean ratios (±SDs) of food spilled to food bitten off in the process of feeding by rats with a unilateral kainate-induced striatal lesion and by vehicle-injected controls.

* $p<0.05$

** $p<0.03$

▼ $p<0.01$

■ $p<0.003$

● $p<0.001$

Mann-Whitney U test, one-tailed.

Periods	Experimental Group of ss (N=6)	Control Group of ss (N=6)
Immediate Preoperative Week	144 ± 6 grams	147 ± 15 grams
* 1st Postoperative Week	101 ± 29	151 ± 16
2nd Postoperative Week	191 ± 8	193 ± 20
24hrs of Feeding following a Period of Food Deprivation	33 ± 3	36 ± 4
During 24hrs of Water Deprivation	16 ± 1	16 ± 3
24hrs of Feeding following a period of Water Deprivation	32 ± 3	33 ± 4

TABLE XXVIII

Means (±SDs) of food intake by rats with a unilateral kainate-induced lesion of the striatum and by vehicle-injected controls.

*$p < 0.002$

Mann-Whitney U test, two-tailed.

For details of the data presented in this table see Appendix F.

Mean water intake by the experimental and control groups is presented in Table XXIX. The values in the table refer to quantities of water (in millilitres) missing from the water-bottles, as it was not possible to measure spillage. There was not a significant difference between the two groups during the 1wk immediately preceding surgery, during the 2nd postoperative week, during the 24hrs of food deprivation, during the 24hrs following the period of food deprivation or during the 24hrs following the period of water deprivation (Mann-Whitney U test), although the experimental group ingested ~~significantly~~ less water than the control group in the 1st postoperative week. ~~($p<0.005$, Mann-Whitney U-test, one-tailed).~~

The mean ratios of faeces passed to food ingested by the kainate-lesioned group of ss and by the vehicle-injected controls during the 1wk just preceding surgery and in the 1st and 2nd postoperative observation weeks are presented in Table XXX. There was not a significant difference between the two groups in any of these periods (Mann-Whitney U test).

Periods	Experimental Group of ss (N=6)	Control Group of ss (N=6)
Immediate Preoperative Week	224 ± 25 grams	197 ± 34 grams
1st Postoperative Week	199 ± 25	223 ± 19
2nd Postoperative Week	288 ± 35	269 ± 20
During 24hrs of Food Deprivation	41 ± 20	28 ± 8
24hrs of Prandial Drinking following Food Deprivation	60 ± 24	44 ± 10
24hrs of Drinking (prandial) following Water Deprivation	63 ± 13	56 ± 3

TABLE XXIX

Means (±SDs) of water intake by rats with a unilateral kainate-induced lesion of the striatum and by vehicle-injected controls.

The inter-group differences are not statistically significant (Mann-Whitney U test).

For details of the data presented in this table see Appendix G.

Periods	Experimental Group of ss (N=6)	Control Group of ss (N=6)
Immediate Preoperative Week	0.33 ± 0.03	0.36 ± 0.02
1st Postoperative Week	0.40 ± 0.06	0.37 ± 0.05
2nd Postoperative Week	0.40 ± 0.05	0.38 ± 0.03

TABLE XXX

Means (±SDs) of ratios of faeces passed to food actually ingested by rats with a unilateral kainate-induced striatal lesion and by vehicle-injected controls.

The differences between the experimental and control groups are not statistically significant (Mann-Whitney U test).

EXPERIMENT II: OPERANT AND SPACE-RELATED BEHAVIOURS FOLLOWING A UNILATERAL KAINATE-INDUCED LESION OF THE STRIATUM

7:2(B) MATERIALS AND METHODS

7:2(B)(i) SUBJECTS

The ss for the present experiment were seven male Wistar albino rats weighing 180-200g at the time of surgery. Throughout the experiment the ss were housed in twos in a reverse daylight room (for further details of the experimental housing conditions see 2:1). The ss had unrestricted access to food and water outside seasons of operant behaviour sessions (see 7:2(B)(ii)). However, they were deprived of food for predetermined periods of time when they had to be prepared for a season of operant behaviour sessions (see 2:2), and had to work for all the food they received while such a season lasted. Moreover, they had no access to water during a food-rewarded operant behaviour session.

7:2(B)(ii) BEHAVIOURAL STUDIES

After an initial seven-day period of disturbance-free orientation in the laboratory housing conditions (2:1) the ss were deprived of food for 48hrs in preparation for training on a food-rewarded operant task as previously described (2:2). After training the ss were given a 25-min data-gathering session in the Skinner box daily for two successive days. Then the ss underwent surgery. A recovery period of seven days followed before postoperative testing in the operant behaviour box was commenced. There were altogether two 25-min data-gathering sessions given one session per day on two successive days, in the postoperative stage of the experiment.

The/

The variables observed and recorded in all data-gathering sessions were; number of effective lever presses made with each forepaw; number of abortive lever presses made with each forepaw; total number of effective lever presses, including those made with both forepaws; number of effective presses made on each lever and number of rotations made in each direction ((a) toward the lesion side, and (b) away from the lesion side). A manually operated many-channelled counting device was used for recording all quantiative observations, and records obtained with the manually operated device in respect of number of effective presses made on each lever were checked against figures provided by electromagnetic counters.

7:2(B)(iii) SURGERY

The surgical procedure is the same as previously described (7:2(A)(iii); 2:5; 2:7; 2:8).

7:2(B)(iv) DISSECTION

The dissection procedure also is the same as previously described (7:2(A)(iv); 2:9).

7:2(B)(v) BIOCHEMISTRY AND HISTOLOGY

Already outlined too are the methods used for the determination of catecholamines, CAT and GAD (7:2(A)(v); 2:12; 2:13; 2:14), and for the cutting and staining of histological sections (2:11).

7:3(B)/

7:3(B) RESULTS

7:3(B)(i) OPERANT BEHAVIOUR

Kainic acid lesion of the striatum contralateral to the forepaw used for most of the preoperative lever-presses caused all the ss to display a clear reversal of forepaw preferences at the test carried out one week after surgery. According to Wilcoxon's matched-pairs signed-ranks test, there was of course a significant difference ($p=0.025$, one-tailed test) between the number of rewarded lever-presses executed with the preferred and unpreferred forepaws before surgery. The postoperative test also showed a significant difference between the forepaws, but in the opposite direction. The patterns of forepaw use in the execution of effective (rewarded) lever-presses before and after surgery are presented in Figure 25. The patterns of forepaw use in the performance of abortive presses (Figure 26) were similar to those of effective forepaw use.

Rate of lever-pressing was significantly depressed by the lesion ($p=0.025$, Wilcoxon's test, one-tailed). The mean number of rewarded lever-presses performed in identical time before and after surgery can be seen graphically represented in Figure 27.

7:3(B)(ii) SPACE-RELATED BEHAVIOUR

Unilateral striatal damage appears to have affected lever choice. Thus prior to surgery the ss operated the ipsilateral lever significantly more times than the contralateral lever ($p=0.025$, Wilcoxon matched-pairs signed-ranks test, one-tailed); but at the postoperative test the reverse was the case ($p=0.025$, Wilcoxon test, one-tailed). Figure 28 depicts the mean number of presses executed on each lever pre- and postoperatively.

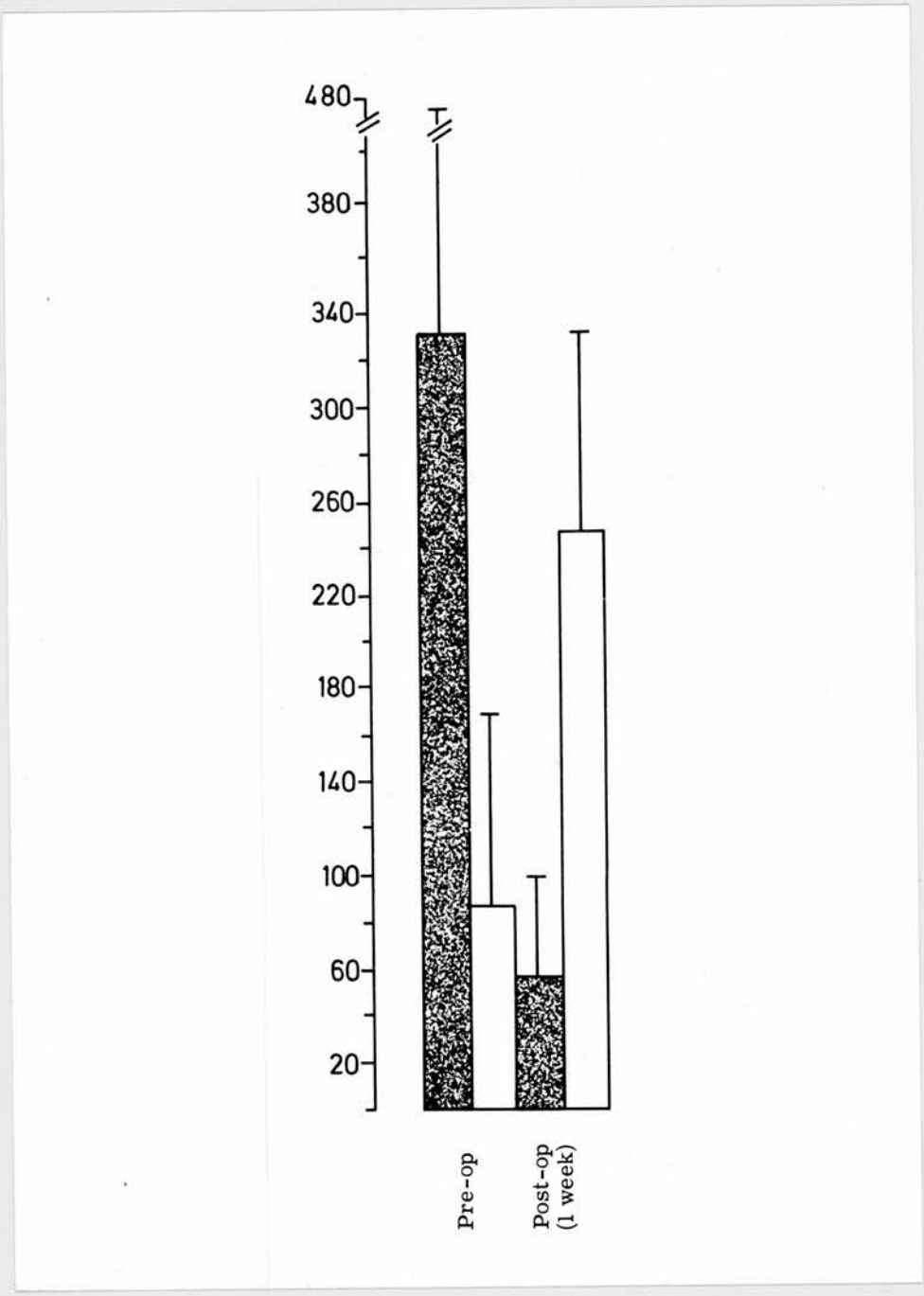


FIGURE 25:

Mean pattern of effective forepaw use displayed by rats before and after a unilateral kainate lesion of the striatum. The columns depict the mean number of effective lever presses made with the preoperatively preferred forepaw (stippled columns) or with the preoperatively unpreferred forepaw (open columns). Each bar represents one SD.

The differences are significant both before and after surgery ($p=0.025$, Wilcoxon matched-pairs signed-ranks test, one-tailed).

Abbreviations: Pre-op., before surgery; post-op., after surgery.

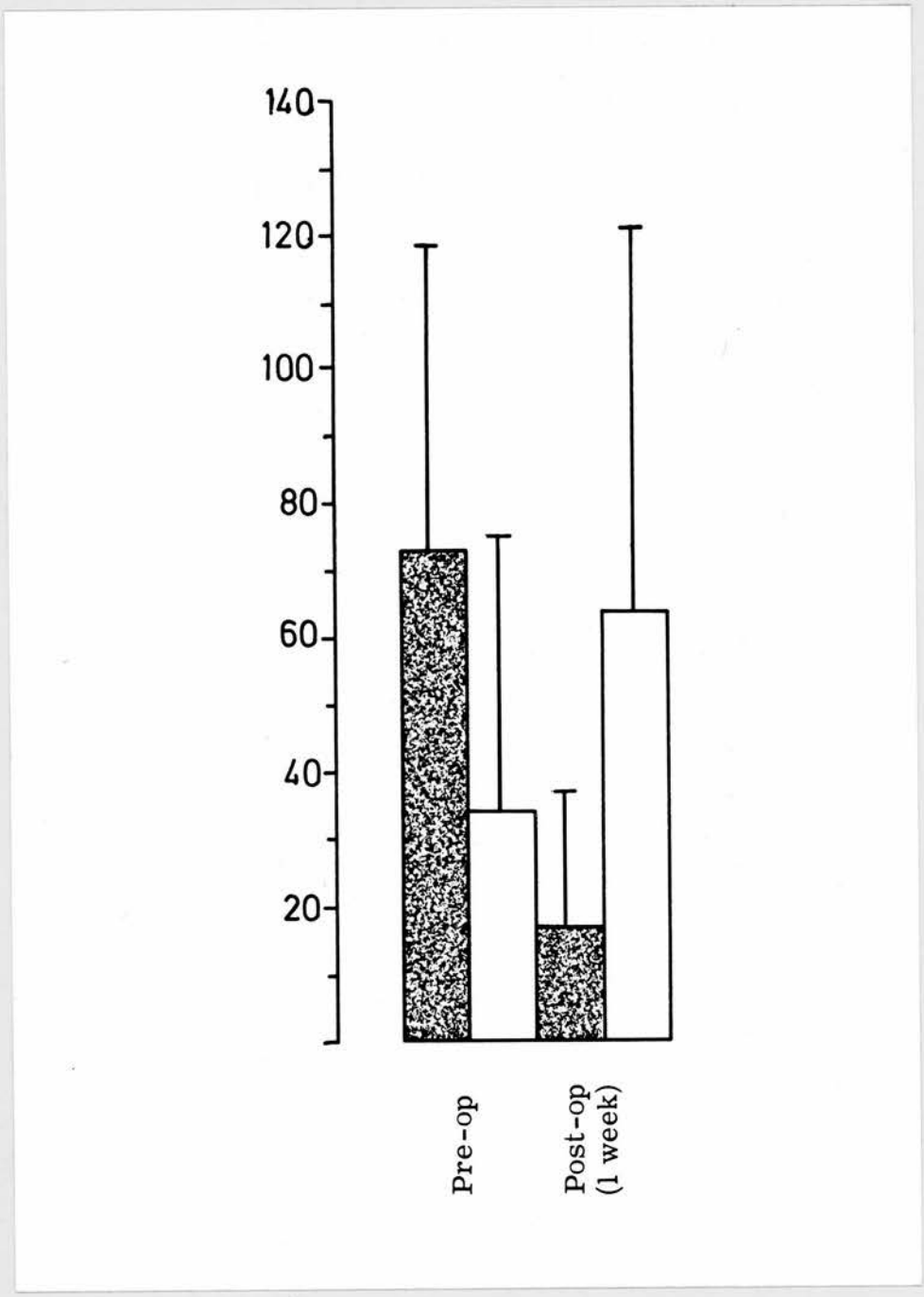


FIGURE 26:

Mean pattern of abortive forepaw use displayed by rats before and after a unilateral kainate lesion of the striatum. The columns depict the mean number of abortive lever presses made with the preoperatively preferred forepaw (stippled columns) or with the preoperatively unpreferred forepaw (open columns). Each bar represents one SD.

The differences are statistically significant both before and after surgery ($p \leq 0.025$, Wilcoxon matched-pairs signed-ranks test, one-tailed).

Abbreviations: Pre-op., before surgery; post-op., after surgery.

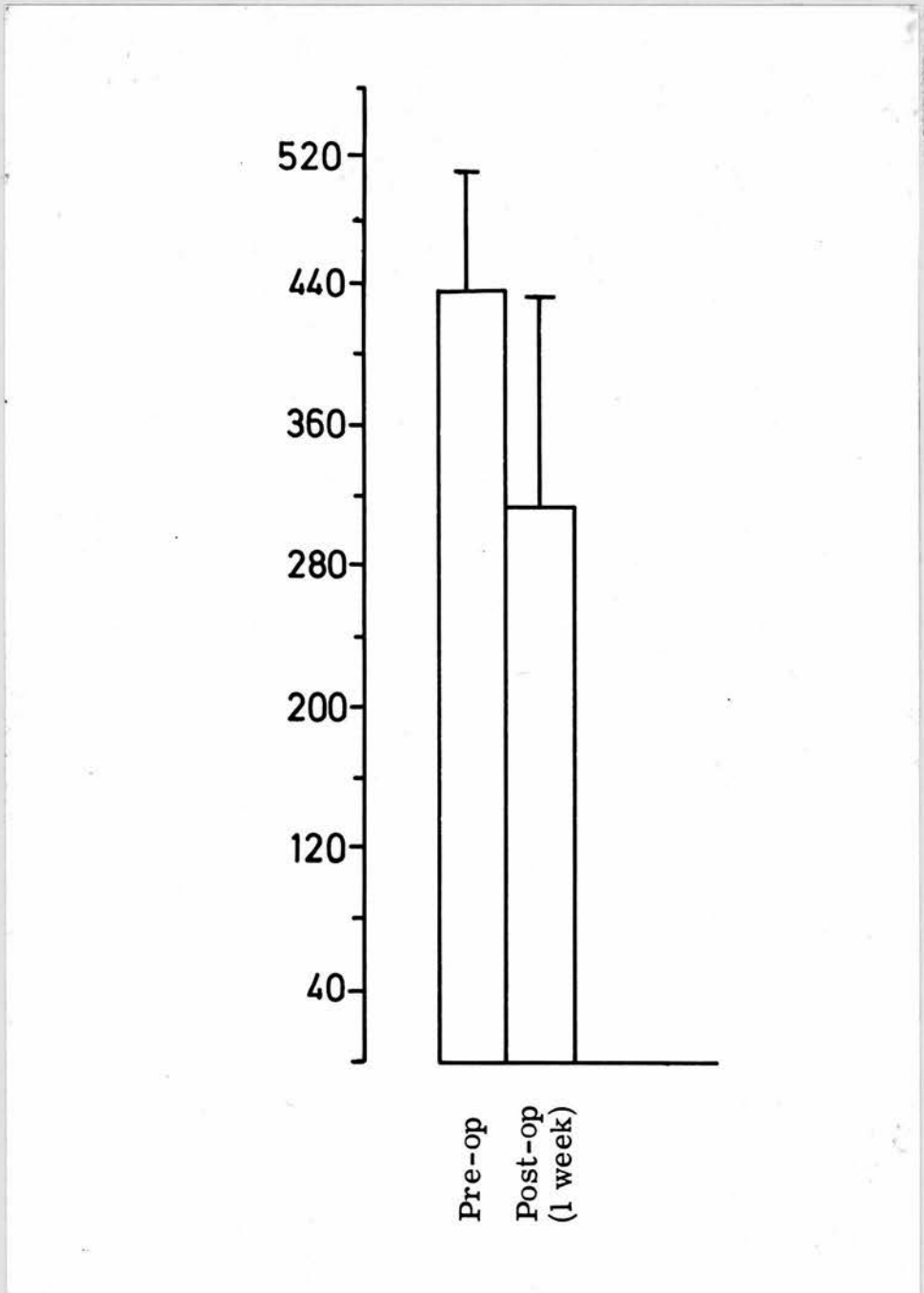


FIGURE 27:

Mean number of effective lever presses made by rats in 50min (two 25-min sessions) before and after a unilateral kainate lesion of the striatum. Each bar represents one SD.

The difference is statistically significant ($p \leq 0.025$, Wilcoxon matched-pairs signed-ranks test, one-tailed).

Abbreviations: Pre-op., before surgery., post-op., after surgery.

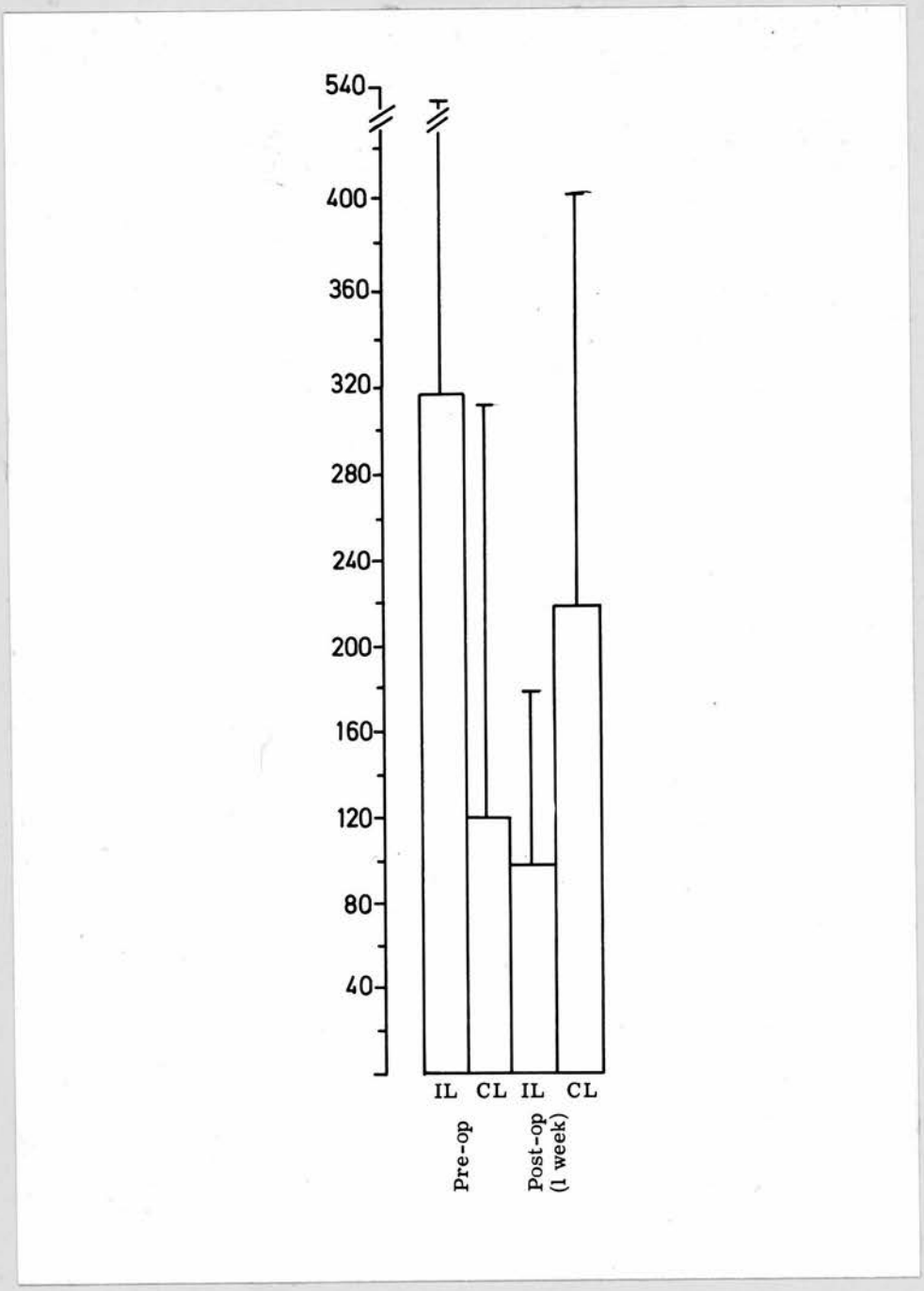


FIGURE 28:

Mean pattern of lever choice displayed by rats in a two-lever Skinner box before and after a unilateral kainate lesion of the striatum. Each column depicts the mean number of effective presses made on the lever ipsilateral to the lesion or on the contralateral lever. Each bar represents one SD.

The differences are statistically significant both before and after surgery ($p=0.025$, Wilcoxon matched-pairs signed-ranks test, one-tailed).

Abbreviations: IL, ipsilateral lever; CL, contralateral lever; Pre-op., before surgery; Post-op., after surgery.

Spontaneous rotation, as recorded during operant behaviour sessions in the Skinner box, was enhanced following surgery (see Figure 29). As the figure shows, postoperative rotation was predominantly ipsiversive to the lesioned striatum. It should be noted that contraversive rotation also occurred; but whereas postoperatively there was a significant difference ($p=0.025$, Wilcoxon test, one-tailed) between the number of ipsiversive versus contraversive rotations observed during the operant behaviour sessions, preoperative records showed no significant difference between the two directions of circling.

7:3(B)(iii) BIOCHEMICAL ASSAY RESULTS

From Table XXXI it can be seen that there were reductions of CAT and GAD activities in the lesioned striatum in all the ss. Activity drop was not consistently greater in the case of either enzyme; in other words, some ss showed a larger drop in striatal CAT than GAD, while for some others the reverse was the case. However, taken together the combined activities of these enzymes suffered a drop of 50% or more in all the ss except one which had a 49% drop.

Nigral GAD activity was not markedly reduced. In fact two ss had a slightly higher GAD activity in the substantia nigra of the lesioned side than in the substantia nigra of the opposite side.

Also limbic forebrain NE was not consistently reduced on the lesion side in two ss (one of the ss with higher GAD activity in the ipsilateral substantia nigra plus one other s).

Ipsilateral limbic forebrain DA was, disappointingly, reduced to some extent in all the ss, although the reduction was only 2% in one s and 5% and 17% in two other ss. One s had a depletion of over 60% in limbic forebrain DA.

There was no significant correlation between the intensity of behavioural impairment and the severity of damage to any one neurochemical system in any of the brain regions sampled (Kendall's tau).

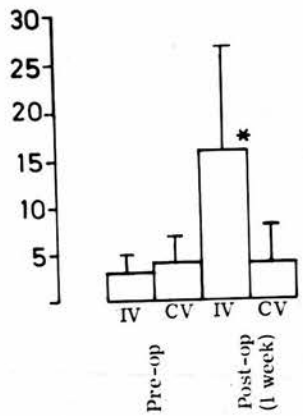


FIGURE 29:

Mean number of rotations performed by rats in an operant behaviour situation in 50min (two 25-min sessions) before and after a unilateral kainate lesion of the striatum. The columns depict the mean number of rotations performed toward the lesion side (IV) or away from it (CV).

*p=0.025

Wilcoxon matched-pairs signed-ranks test, one-tailed.

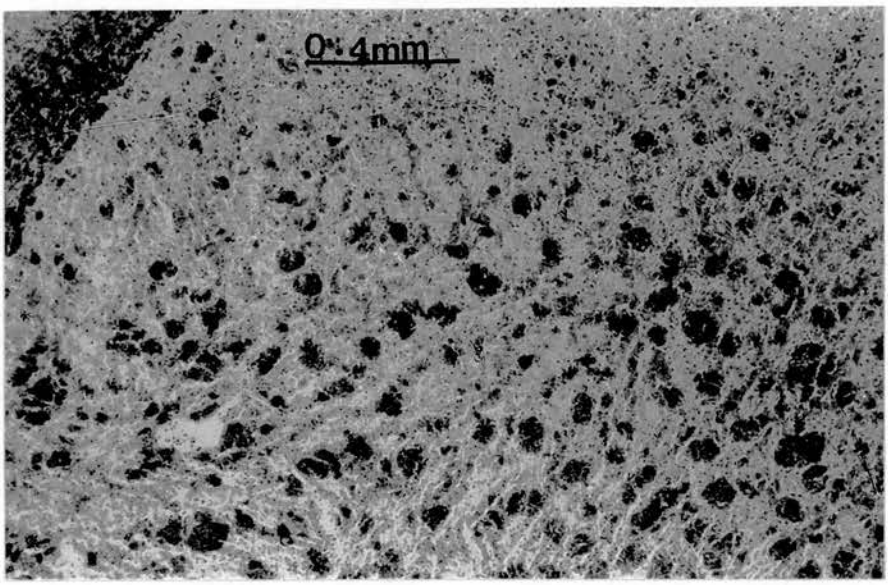
Abbreviations: IV., ipsiversive; CV., contraversive; Pre-op., before surgery; Post-op., after surgery.

Subject Number	% Loss in Striatal CAT	% Loss in Striatal GAD	% Loss in Nigral GAD	% Loss in "LIMBIC" DA	% Loss in "LIMBIC" NE
*A	80	70	47	63	68
B	44	65	56	17	19
C	72	91	0	2	0
D	53	46	36	34	24
E	73	27	0	50	26
F	49	67	34	5	0
G	85	64	47	57	40
Mean±SD	63 ± 16	60 ± 22	29 ± 24	28 ± 23	18 ± 16

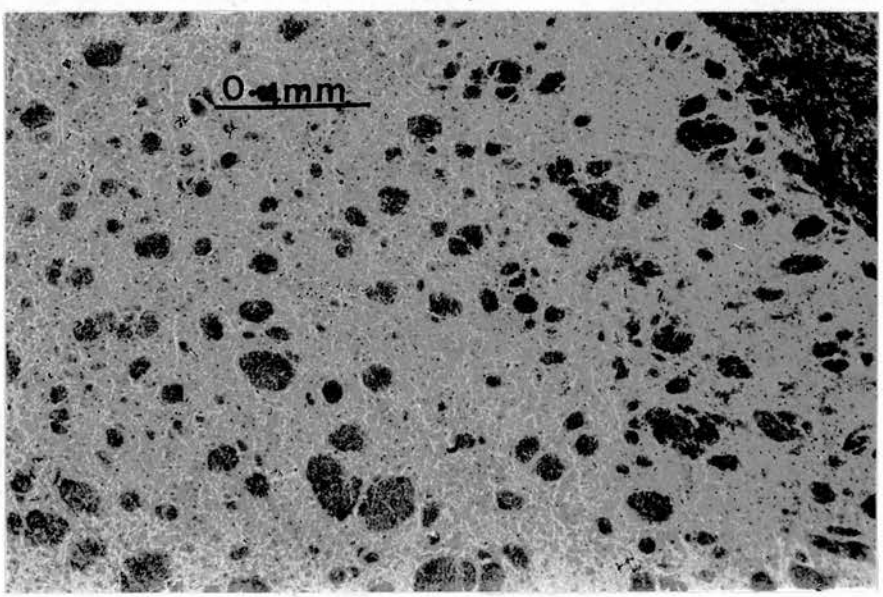
TABLE XXXI

Some neurochemical deficits in the lesioned hemisphere of rats sustaining a unilateral kainate-induced damage of the striatum contralateral to the predominantly used forepaw.

*Because this s suffered a huge reduction in limbic forebrain ("LIMBIC") levels of catecholamines it was excluded from all analysis of data relating to the neurochemical and behavioural effects of the lesion.



A



B

FIGURE 30:

Photomicrographs showing the striatum on each side of the brain of a rat given a unilateral intrastriatal injection of kainic acid.

Plate A: lesioned striatum

Plate B: intact striatum

Abbreviations: RCC., Radiatio corporis callosi.

7:3(B)(iv) HISTOLOGY RESULTS

Microscopic examination of the histological sections prepared from the brains of the ss by a procedure described earlier (see 2:11) revealed no damage to structures posterior to the striatum in any of the animals. Figure 30 shows the apperances of the lesioned and unlesioned striata in an s presenting evidence of striatal damage in the portion of the brain set aside for histological study.

Photomicrographs showing the pallidum on each side of the brain of a typical rat that received a unilateral intrastriatal injection of kainic acid without sustaining pallidal damage are displayed elsewhere (Figure 22).

7:4 DISCUSSION

7:4(i) UNILATERAL STRIATAL DAMAGE AND BODY WEIGHT REGULATION

From Table XXIV and Figure 24 it can be seen that the acute effect of surgery on body weight is more pronounced in the group of ss receiving a unilateral microinjection of kainic acid into the striatum than in the vehicle-injected control group. The difference between the two groups in this regard is statistically significant. This observation is reminiscent of the comparative acute effects of surgery in the 6-OHDA-treated and control groups in a previous experiment (see Figure 6). However, unlike the 6-OHDA-treated group in the earlier study the depression of body weight observed following surgery was not sustained in the kainate-injected group in the present experiment. Thus, by the end of the recorded-observation period the kainate-injected group had outstripped the control group in weight, even although their preoperative mean weight had been somewhat lower than that of the control group.

The difference between the two groups in weight gained in the last week of recorded observation (see Table XXIII) was statistically significant. The apparent facilitatory effect of intrastriatal kainate administration on the rate of weight increase is difficult to explain. However, it is interesting to note that whereas interrupting the nigrostriatal DA pathway unilaterally through 6-OHDA microinjection into the MFB of one hemisphere produces a chronic depression of body weight (Baez et al., 1977; also Figure 6), the postsynaptic disruption of the nigrostriatal system on one side through unilateral kainate administration into the striatum, which does not significantly cut off DA supply to the striatum and other brain areas (Schwarcz and Coyle, 1977), fails to produce a similar effect on body weight.

Even more interesting is the evidence from the present experiment that the long-term facilitatory effect of intrastriatal kainic acid administration on body weight is not entirely, if at all, due to over-eating. Thus, for example: (a) the kainate-injected group of ss ingested significantly less food (Table XXVIII) and drank significantly less water (Table XXIX) than controls in the immediate postoperative week and yet there was no significant difference between the two groups in body weight increases in that period (Table XXIII); and (b) there was no significant difference between the two groups in food or water intake in the second postoperative week, yet the kainate-injected group gained significantly more weight than controls in that period. Furthermore, although there was not a significant difference between the two groups of ss in weight lost as a result of 24hrs of food deprivation or in weight achieved during 24hrs of feeding at the end of the food-deprivation period one finds that the total increase in weight displayed

by/

by the kainate-injected group in the 48hr period was signifcantly greater than that observed in the control group in the same period (see Table XXV). It appears that the kainate-injected group lost less weight in the food-deprivation period and gained more weight following food-restoration than did the control group, with the additive result that the total weight increase in the 48hrs under consideration was significantly higher for the kainate-injected group.

If the notion that animals feed to meet a body weight target is correct (Boyle and Keesey, 1975; Powley and Keesey, 1970; Teitelbaum, 1961; see also 3:4(i)) the kainate-injected rats must have been adopting a new pattern of body weight targetsthat is different from, and on a higher level than, the pattern adopted by controls. Since the neurochemical and structural effects of intrastriatal kainate administration reflect primarily the disruption of striatal intrinsic neuronal populations, it seems reasonable to conclude that the striatum contains neurons concerned with the inhibitory control of body weight, and that the integrity of this neuronal population is essential for the maintenance of body weight at normal levels.

7:4(ii) UNILATERAL STRIATAL DAMAGE AND FOOD SPILLAGE

The effect of unilateral kainate-induced lesion of the striatum on food spillage (see Table XXVII) is similar to that associated with unilateral 6-OHDA-induced interruption of the nigrostriatal DA pathway (Table V). Thus, like the 6-OHDA-injected rats of the earlier experiment, the kainate-injected ss of the present feeding experiment spilled more food than controls per unit amount bitten off in the process of/

of eating. The similarity between the effects of the two kinds of lesion on food spillage appears to reflect a common function shared by the nigrostriatal DA pathway and the striatum. It has been proposed on the strength of results presented in Chapter 3 that the abnormally high food-spillage rate observed in animals with a unilateral nigrostriatal pathway lesion represents an impairment of sensorimotor functions (3:4(i)). It may be recalled that in the experiment reported in Chapter 3 6-OHDA lesioned rats trained to operate a lever for food reward displayed an incapacity to use the forepaw contralateral to the lesion side (see Figure 7a(i)). It may also be recalled that the apparent contralateral forelimb incapacitation by unilateral nigrostriatal damage was confirmed in a later experiment in which animals lesioned on the side opposite to the predominantly used forepaw displayed a reversal of forepaw preferences when tested postoperatively (see Figure 9). In the present chapter a similar result was obtained with unilateral administration of kainic acid (Figure 25). It seems reasonable, therefore, to conclude that the nigrostriatal DA pathway and some groups of neuronal perikarya intrinsic to the striatum share a common function in sensorimotor control. It appears that the central control of sensorimotor function is exerted through a lateralised complex network of which the nigrostriatal DA pathway and the striatum are components. The integrity of this network seems essential for efficient sensorimotor behaviour. Thus if the network is interrupted sensorimotor dysfunction results whether the interruption occurs at the pallidum (Levine et al., 1971) the entopeduncular nucleus (Levine and Schwartzbaum, 1973), the nigrostriatal DA pathway (Marshall et al., 1974; see also Figure 7a(i) and 9), the striatum (Hansing et al., 1968) or elsewhere.

7:4(iii) UNILATERAL STRIATAL DAMAGE AND OPERANT BEHAVIOUR

It has been demonstrated in a previous study that microinjection of the catecholamine-specific neurotoxin, 6-OHDA, into the MFB on the side opposite to a forepaw used for most lever presses in a food-rewarded operant behaviour arrangement produces in rats a reversal of forepaw preferences (see Figure 9). Following further work this lesion-induced effect was interpreted as reflecting an interruption of a neural transmission pathway rather than DA loss per se (5:4(i)). The results of the present study have shown that discrete ablation of a sufficiently large proportion of neuronal perikarya intrinsic to the striatum contralateral to a preoperatively preferred forepaw produces a similar effect on forepaw preferences (Figure 25). Thus, disrupting the nigrostriatal system at the postsynaptic level would appear to be as effective as presynaptic disruption in impairing sensorimotor control. This finding seems significant for the hypothesis proposed in Chapter 5 that nigrostriatal control of rotational behaviour and forelimb use is exercised on different principles, if one also compares the effects of lesion on rotational behaviour in the experiments reported in Chapter 4 (see Figure 13) and the present chapter (see Figure 29). In the earlier study, in which 6-OHDA damage of the MFB on one side caused a huge loss of DA in the corresponding striatum, spontaneous rotation was enhanced to an exaggerated degree and was exclusively ipsiversive, whereas in the present experiment in which DA supply to the striatum and other structures should not be markedly reduced, spontaneous rotation was only moderately increased and not entirely ipsiversive. In other words, it has been possible, through the destruction of a sufficient proportion of those neuronal perikarya in the striatum which are involved in sensorimotor control,/

control, to produce forelimb dysfunction that is strikingly similar to that associated with 6-OHDA-induced lesion of the nigrostriatal dopamine pathway without precipitating a comparable degree of effect on rotational behaviour.

The finding that striatal damage causes limb dysfunction is by no means new (see Hansing et al., 1968). What the present study has done in this regard is to demonstrate that the sensorimotor loss observed by previous investigators following electrolytic destruction of the striatum was not just due to disruption of fibres and non-neural tissue present in the striatum.

In the present experiment the patterns of forepaw use in the performance of abortive lever-presses were similar to those of effective forepaw use before and after surgery. This observation is identical to those made in previous studies (see Figures 7a(ii), 10 and 15a(ii)), and appears to confirm the view that the loss of "spontaneous" voluntary control of forelimbs following nigrostriatal damage is total and does not permit continued spontaneous (even though abortive) use of the affected limb. This view, if correct, predicts that any attempts to retrain animal or human victims of nigrostriatal damage in effective sensorimotor control would have to <u>elicit</u> in some way the use of the affected motor organs before practice-related learning can occur.

As Figure 27 shows, the rate of lever-pressing showed a drop after surgery in the present study. If one compares this figure to Figure 11 it can be seen that the drop in rates of lever-pressing exhibited by contralaterally lesioned ss following 6-OHDA lesion of the MFB was similar in size to that observed after striatal damage. Both drops are greater than that displayed by the ipsilaterally lesioned ss in the

6-OHDA/

6-OHDA experiment. It seems then that indeed the difference in rate reduction between the ipsilateral and the contralateral groups in the 6-OHDA experiment was due to the fact that the contralaterally lesioned ss had to learn to use a new paw rather than to any differential effect of striatal DA loss.

7:4 (iv) UNILATERAL STRIATAL DAMAGE AND LEVER PREFERENCE IN A TWO-LEVER OPERANT BEHAVIOUR SITUATION

Unlike in previous experiments in which a unilateral nigrostriatal pathway lesion induced by 6-OHDA failed to produce a consistent effect on lever preference (see Figures 7c and 12), unilateral striatal damage appears to have affected lever choice (Figure 28). Whereas animals tend to rotate predominantly in the ipsiversive direction following a unilateral striatal (Figure 29) or nigrostriatal (Figure 13) lesion, unilateral striatal damage produces a contralateral lever preference. It is evident, therefore, that the kind of spatial behaviour represented by lever preference in a two-lever Skinner box of the design used in these experiments is not directly controlled by the nigrostriatal DA system in the way that rotational behaviour is directly controlled (see 5:4(i)).

7:4(v) NEUROCHEMICAL CONSIDERATIONS

The biochemical results in the experiment on forepaw use (see Table XXXI) indicate that the induction of limb dysfunction through striatal damage can be associated with a reduction of striatal CAT activity or of striatal GAD activity, or both. Thus the involvement of both cholinergic and GABAergic neuronal perikarya intrinsic to the striatum in/

in sensorimotor control is a probability. Although the exact organisation of these neuronal populations within the striatum is at present not clear, the important thing from the point of view of sensorimotor control appears to be the maintenance of the neural transmission chain responsible for that control. A break in the chain at any level (including the striatum) would appear to be the determining factor in the production of sensorimotor dysfunction.

Damage to the striato-nigral GABAergic pathway, a neural connection that is known to exist (Voneida, 1960; Szabo, 1962) is not involved in the behavioural effects of striatal lesion which were observed in the present studies since such damage was by no means universal among the ss and was small where it occurred (see Tables XXII and XXXI). For a similar reason, damage to NE fibres supplying forebrain areas which surround or are rostral to the striatum cannot be responsible for the behavioural results of the experiment. The question of limbic forebrain DA involvement is a bit more tricky since most of the ss sustained a certain amount of loss in DA content of the ipsilateral limbic forebrain area (Tables XXII and XXXI). However, the biochemical results of one of the experiments reported in Chapter 4 (Experiment I) had shown that one of the partially lesioned control ss had a limbic forebrain DA loss of 62% (associated with 66% loss of striatal DA) and another had a limbic forebrain DA loss of 58% (associated with 69% loss of striatal DA), and both ss had failed to display forelimb dysfunction at the postoperative tests. These reductions of limbic forebrain DA are higher than those suffered by some of the animals of the present experiments. It seems reasonable, therefore, to conclude that the sensorimotor deficits observed following kainic acid lesion of the striatum are not related to loss of limbic forebrain DA by the ss. This interpretation agrees with the model proposed

by Iversen (1977) which dissociates the functions of the striatal and mesolimbic DA systems. According to that model the nigrostriatal DA system, by virtue of its close connections with the major motor output systems, is directly concerned with the stimulation of motor behaviour, whereas the mesolimbic system, owing to limbic and hypothalamic influences, plays a primarily motivational role.

CHAPTER 8

GENERAL DISCUSSION

8:1 THE NIGROSTRIATAL DOPAMINE SYSTEM AND SENSORIMOTOR FUNCTION

The results from several experiments reported in this thesis strongly suggest that the nigrostriatal DA system is involved in the sensorimotor control of behaviour (see Figures 7a(i) and 9). As Figure 9 shows, if rats are trained to push a lever for food in an operant behaviour situation and then given a 6-OHDA microinjection into the MFB contralateral to the preferred forepaw they exhibit a reversal of forepaw preferences when tested postoperatively, whereas forepaw preferences are not affected in ipsilaterally lesioned animals or in controls. This finding is in agreement with an observation made in the experiment in which rats with a 12wk old lesion of the MFB on one side were trained to operate the lever for food reward. All the lesioned ss that acquired the lever-pressing response used only the forepaw on the same side as the lesion, to the utter exclusion of the contralateral forepaw, whereas three out of six control ss displayed predominant or exclusive use of the forepaw contralateral to the vehicle-injected MFB (Figure 7(a)). These results suggest that the contralateral forepaw is incapacitated selectively following a unilateral microinjection of 6-OHDA into the MFB, a suggestion supported by the observation that most of the lesioned animals tended to have their contralateral forelimb hanging limply down between the grids of the Skinner box floor during lever pressing.

In other words, whatever the important system that is damaged as a result of 6-OHDA microinjection into the MFB, it must be, like the pallidum (Levine et al., 1971), the entopeduncular nucleus (Levine and Schwatzbaum,/

Schwatzbaum, 1973) and the striatum (Hansing et al., 1968; see also Figure 25) part of a lateralized system controlling forelimb use.

It can be recalled by referring to Table IX that MFB administration of 6-OHDA reduced catecholamine levels in the rostral regions of the brain. Most severely depleted were striatal and limbic forebrain DA levels. In this regard, it should be noted that although there are strong indications of nigrostriatal dopaminergic involvement in the sensorimotor control of behaviour (Marshall et al., 1974; Hansing et al., 1968; see also Figure 9) the nucleus accumbens, which is a limbic structure with a rich supply of DA appears to be involved in locomotor activity in rats (Fibiger, Fibiger and Zis, 1973; Jackson, Anden and Dahlstrom, 1974; Pijnenberg and Van Rossum, 1973). It is not, therefore, possible solely on the strength of the 6-OHDA experiments in this thesis to conclude that the disruption of the nigrostriatal DA pathway was or was not responsible for the observed incapcitation of the contralateral forelimb in animals sustaining a unilateral lesion of MFB. Disruption of the DA system supplying the "limbic forebrain" area, or even of the NE system which supplies the striatum and the origin and function of which are at present not clear, might conceivably be responsible for this effect.

The kainic acid experiments (Chapter 7) were designed primarily to deal with this interpretational difficulty. As Figure 25 shows, all the animals, which suffered a kainate ablation of the neuronal perikarya intrinsic to the striatum on the side contralateral to the preoperatively preferred forepaw, exhibited a reversal of forepaw preferences when tested postoperatively on an operant task acquired prior to surgery. This/

This observed effect of lesion is precisely the same as that seen in animals with a 6-OHDA lesion of the MFB opposite to the preoperatively preferred forepaw (Figure 9). However, kainate ablation of striatal intrinsic neuronal perikarya has been reported to spare axon terminals and fibres of passage (Schwarcz and Coyle, 1977), and in the kainate lesion experiments here presented the reductions in limbic forebrain DA were not so severe (see Tables XXII and XXXI) as had been observed in animals with a 6-OHDA lesion of the MFB (Table IX). In fact, some of the kainate-lesioned animals, which displayed an indisputable effect of lesion on forepaw use, showed less reduction in limbic forebrain DA than certain other ss which had sustained a partial lesion of the MFB on the contralateral side and had displayed no effect on forepaw preferences.

Moreover, kainate ablation of striatal intrinsic neuronal perikarya obviously disrupts the nigrostriatal DA system postsynaptically by removing the postsynaptic receptors of DA and/or other links in the chain of neural transmission of impulses reaching the striatum via the nigrostriatal DA pathway. The additional use of a kainate lesion procedure disrupting the nigrostriatal DA system postsynaptically appears therefore to have confirmed the involvement of this system in the sensorimotor control of behaviour, although it does not necessarily show that sensorimotor performance would be unaffected by an extensive selective disruption of the system supplying DA to the limbic forebrain area, notably the nucleus occumbens. The complementary use of both the 6-OHDA and the kainic acid techniques in the investigation of nigrostriatal dopaminergic involvement in sensorimotor control does confrim furthermore the viewpoints (see 5:4(i)) that the cardinal principle in this control is that of uninterrupted transmission of relevant nerve impulses on a network which includes, among other components, the pallidum/

pallidum, the entopeduncular nucleus, the striatum and the nigrostriatal DA pathway.

Concerning the precise role of the nigrostriatal DA pathway in the sensorimotor control of behaviour, it must be admitted that the present project has not determined that. It has already been proposed that the deficit which results from a lesion of the nigrostriatal DA system is "an interruption of sensory motor ingetration" (Ranje and Ungerstedt, 1977). This hypothesis does not, however, explain whether the nigrostriatal DA pathway is a sensory or motor pathway. Also it is known that the nigrostriatal DA pathway provides a link between the substantia nigra and the extrapyramidal system (Bedard et al., 1969), and is, therefore, closely associated with the extrapyramidal system, a network importantly involved in motor behaviour; but even this fact does not necessarily demonstrate whether the nigrostriatal DA bundle is a sensory pathway or a motor pathway. It seems that the unravelling of the precise contribution of the nigrostriatal DA pathway in the sensorimotor control of behaviour will have to await further work. One possible approach to the problem could be to investigate the involvement of the nigrostriatal system in purely sensory functions, with particular reference to the sense of touch - using intact animals and animals with a 6-OHDA lesion of the nigrostriatal pathway. If such an experimental design should demonstrate that the nigrostriatal DA system was not involved in those sensory functions associated with forelimb use that would suggest that the forelimb incapacitation observed following nigrostriatal or striatal damage reflects a motor deficit. Perhaps a good initial experiment could be to investigate the electrophysiological activity of striatal neurons following a tactile sensory input,/

input, in intact animals and in animals with a nigrostriatal lesion.

8:2 CLINICAL IMPLICATIONS OF THE SENSORIMOTOR STUDIES

One of the clinical implications of the sensorimotor studies presented herein is represented in the finding that efficient sensorimotor behaviour is more than a matter of stimulating the DA receptors. It is known that drugs which increase activity in central catecholamine synapses enhance whereas drugs which reduce activity in these synapses depress, electrocortical arousal and behavioural responsiveness (Jouvet, 1972). It is also known, however, that high doses of the direct-acting DA receptor stimulant drug, apomorphine, or of the indirect stimulant, amphetamine, produce stereotypy, a form of behaviour that cannot be described as reflecting efficient sensorimotor function. In this thesis (see Figure 16) it has been demonstrated that it is not possible to restore in rats the ability to use a forepaw incapacitated by a unilateral nigrostriatal lesion by just administering apomorphine to them even at a dose that elicits contraversive circling and at the same time permits the animals to operate a lever for food in an operant behaviour situation. In other words, it has been shown that whereas the direction of circling is determined by the relative levels of activity at the DA postsynaptic receptors in the two hemispheres in animals with a unilateral nigrostriatal lesion, forepaw preference in the performance of operant responses is not similarly determined in such animals, even if they had prior to surgery displayed a preference for the incapacitated forepaw. Thus general arousal in intact animals and rotational behaviour in animals with a unilateral nigrostriatal lesion may be directly and simply determined by activity in the DA synapses, but the sensorimotor control of forelimb use involves more than DA

receptor/

receptor stimulation. The sensorimotor control of behaviour appears to be ultimately dependent upon the uninterrupted transmission of relevant information rather than upon DA postsynaptic receptor stimulation per se (see 5:4(i)).

The neurological disorder of parkinsonism is associated with the degeneration of the nigrostriatal DA system (Ehringer and Hornykiesicz, 1960; Hassler, 19 8; Hornykiewicz, 1966; Tretiakoff, 1919), and has been characterized as a "striatal dopamine deficiency syndrome" (Hornykiewicz, 1973). A difficulty in initiating voluntary movements is one of the chief symptoms of parkinsonism. Seeing that activity in central DA synapses has been implicated both in the arousal component of behaviour (Stricker and Zigmond, 1976) and in rotational behaviour (Anden et al., 1966; Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1969; Ungerstedt, 1971c; 1971e) it is not surprising that pharmacologically induced rotation has been used as the behavioural index of therapeutic effectiveness in the development of new anti-parkinsonian drugs (e.g. Fuxe and Ungerstedt, 1976).

The assumption at the root of the adoption by these authors of the "6-OHDA rotation model" appears to be that drugs which can functionally replenish the DA supplies of the striatum - an effect readily reflected in the reversal of the steady-state direction of circling in unilaterally lesioned animals - should eliminate the behavioural handicaps associated with nigrostriatal damage.

The snag with this model in the development of antiparkinsonian drugs is that a drug which elicits contraversive rotation in animals with a unilateral nigrostriatal lesion will not necessarily restore effective limb use in a condition of sensorimotor dysfunction due to degeneration of/

of the nigrostriatal system (see Figure 16). At best such a drug will achieve enhanced alertness, which is not really a cure for an inability to use the musculature of the limbs, the mouth and other regions of the body. It may be useful for the treatment of parkinsonism, therefore, to develop ways of curing the sensorimotor dysfunction, as well as the arousal deficit, known to be associated with nigrostriatal damage.

A second clinical implication of the sensorimotor studies may be appreciated by recalling that one of the nine rats sustaining a nigrostriatal lesion on the side contralateral to the preoperatively preferred forepaw in the experiment reported in 4:2(A) and 4:3(A) exhibited a spontaneous recovery of its preoperative forepaw preference when tested eight weeks after surgery. The recovery observed in that animal is evidently functional rather than structural since the catecholamine assay results (Table IX) show that the 6-OHDA lesion of the MFB was as effective in the case of that particular s as in other contralaterally lesioned ss which did not show a similar recovery. The observed recovery probably reflects some kind of plasticity of the central nervous system. If the forelimb dysfunction which has been demonstrated following a nigrostriatal lesion actually represents in animals an aspect of parkinsonism in humans, then the observed spontaneous recovery by an animal of the capacity to use a lesion-incapacitated forepaw may in turn represent a flash of hope that under appropriate conditions parkinsonian patients may get to display normality in the performance of voluntary movements. This hope appears to be strengthened by the observation in a different experiment (4:2(C) and 4:3(C) that of four animals trained in an operant behaviour situation two weeks after surgery, two displayed a preference for the forepaw on the side contralateral/

contralateral to the lesioned nigrostriatal system. In this regard it may be recalled that in yet another experiment (see 3:2(ii) and 3:3(i)) five rats trained for the first time 12wks after sustaining a unilateral nigrostriatal lesion used only the ipsilateral forepaw to operate the levers in the Skinner Box to obtain food. It seems, therefore, that the age of a nigrostriatal lesion is an important factor in determining whether or not it effectively disrupts the performance of sensorimotor responses acquired after the damage. By implication, it should be possible to train parkinsonian patients to perform sensorimotor responses efficiently, especially if the disease is diagnosed early. In other words, it might be found that some kind of rehabilitation training could exploit the evident plasticity of the central nervous system to help neurological patients.

8:3 FOOD SPILLAGE AS AN INDEX OF SENSORIMOTOR DYSFUNCTION

From Table IV it can be recalled that rats with a unilateral nigrostriatal lesion spill more food than controls per unit amount bitten off in the process of feeding. Also it may be recalled that a selection of lesioned ss from that experiment were trained in an operant behaviour situation and displayed an exclusive preference for the forepaw on the lesion side, whereas the control group did not show a similar preference for either forepaw. Thus the lesioned animals may have suffered a deficit in the capacity to use the musculature of the contralateral forelimb, and probably also of other areas of the body, including parts of the mouth region. In other experiments, animals sustaining a unilateral kainic acid lesion of the striatum exhibited an incapacitation of the forelimb contralateral to the lesion side (see Figure 25) and another set of animals/

animals that were similarly lesioned displayed a higher rate of food spillage than controls (see Table XXVI). These results were reminiscent of the effects of a unilateral nigrostriatal damage on forelimb use (see Figure 9) and food spillage (see Table IV). Other factors not directly investigated in the present project, notably possible emotional effects of lesion, could have contributed to the abnormally high rate of food spillage observed in the lesioned groups of ss in these experiments; for example, if the lesions were to enhance anxiety levels in rats, such an effect might lead to increased food spillage. It cannot, however, be denied that mastication of food is a sensorimotor process and that the incapacitation of forelimbs such as accompanies nigrostriatal or striatal lesions is not likely to be an effect restricted to forelimb use. It seems justifiable, therefore, on the basis of the experiments mentioned, to regard the rate of food spillage as a genuine index of the effectiveness of a lesion that should interrupt the central neural network controlling sensorimotor behaviour (see 3:4(i)).

8:4 THE NIGROSTRIATAL DOPAMINE SYSTEM AND BODY WEIGHT REGULATION

In the light of the relevant results from several of the experiments presented in this thesis (see Figures 6 and 24; Tables I and XXIII) it appears that the nigrostriatal DA system is involved in some way in the regulation of body weight. Thus, to begin with, rats sustaining a nigrostriatal lesion as a result of unilateral microinjection of 6-OHDA into the MFB displayed a steep decline in body weight in the immediate postoperative days and remained underweight throughout the observation period in the study described in Chapter 3(see Figure 6). This observation corroborates the report of Baez et al., (1977) (for some details/

details of their study, see 3:1(i)). In the experiment carried out by the present author both the immediate post-operative weight loss and the subsequent deficit in the rate of weight gain by the lesioned animals were associated with a marked drop in ad lib. food intake (see Table V). Also food intake by such animals following a period of food deprivation was less than that recorded in the case of control ss (see Table IV). The lesioned animals displayed, moreover, an abnormally high rate of food-spillage in the process of eating (Table IV) and this phenomenon appears to reflect a sensorimotor deficit (see 3:4(i)). However, since the lesioned animals were shown to be able to compensate for a food deficit due to deprivation as argued in an earlier discussion (3:4(i)), the sustained reduction in food intake, which the lesioned animals displayed, cannot be adequately accounted for by the fact that they spilled more of the food they bit off in the process of feeding than did controls. They could have eaten more from day to day in spite of their abnormal food-spillage habits if only they had needed to do so. It appears that animals with a unilateral nigrostriatal lesion, and unlesioned animals as well, eat to meet a homeostatic need of some kind that is reflected in the body weight. When an animal is prevented from reaching the physiologically determined target, say through food deprivation, it is set to consume more food than normal in order to meet that target. The main difference between normal rats and rats with a unilateral nigrostriatal pathway lesion in respect of food intake and body weight regulation seems to be that a unilateral nigrostriatal pathway lesion lowers that target with the result that lesioned animals require less food than unlesioned ones to meet their physiologically determined set- points in body weight.

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The precise mechanism whereby the nigrostriatal DA system exerts its controlling influence on body weight is not clear from the 6-OHDA study just discussed. However, from the combined results from two other experiments employing a unilateral kainate lesion of the striatum (7:2(A), 7:3(A), 7:2(B), 7:3(B)) and prolonged haloperidol treatment (6:2(A), 6:3(A), 6:2(B), 6:3(B)) respectively, it appears that the nigrostriatal DA system exerts its influence on body weight and food intake through the action of DA on postsynaptic receptors in the striatum. From Figure 24 it can be seen that following surgery rats with a unilateral kainate lesion of the striatum displayed a marked loss of weight for a few days but thereafter gained weight at a tremendous pace until they actually outstripped the control ss in weight. In the first postoperative week the lesioned group appear to have gained an unusually large amount of weight for the quantity of food ingested and in the second postoperative week they were superior to the control group both in the amount of food ingested and in body weight gain.

It seems, therefore, that a unilateral ablation of striatal intrinsic neuronal perikarya has an effect on body weight and food intake that is opposite to the effect of a unilateral nigrostriatal lesion. The effect of chronic haloperidol administration on body weight resembles that of a unilateral kainate lesion of the striatum in being facilitatory. Prolonged haloperidol administration would appear to functionally simulate in its effect the destruction of some neorons intrinsic to the striatum. It seems reasonable, therefore, to suggest that there might be neurons with their perikarya localized within the striatum which exert an inhibitory control on body weight, with the result that when they are ablated or rendered

functionally ineffective through pharmacological manipulation weight gain is facilitated. DA is known to exert an inhibitory action on a large number of neurons in the striatum (Bloom et al., 1965 ; Connor, 1970; McLennan and York, 1967). Such an inhibitory action on a neoronal system functioning to limit body weight appears to be necessary for the maintenance of a normal pattern of body weight increase. It is, therefore, not surprising that interrupting the supply of DA to the striatum by placing a lesion in the nigrostriatal DA pathway leads to a chronic deficit in body weight.

8:5 DOPAMINE RECEPTOR BLOCKADE AND SENSORIMOTOR FUNCTION

The depression of food spillage by halopidol treatment (Tables XIV and XVIII) is a worrying observation, viewed in the light of the proposal put forward elsewhere in this thesis (3:4(i)) to the effect that the high rate of food spillage displayed by animals with a unilateral nigrostriatal lesion reflects a sensorimotor deficit. This is because haloperidol is a blocker of DA receptors (Anden et al, 1970) and would as such be expected to interfere with the transmission of neural impulses including any that might be relevant to the sensorimotor control of behaviour.

However, it is known that the capacity to use the mouth effectively is impaired following lesions of the nigrostriatal pathway (Marshall et al., 1974) or the pallidum (Levine and Schwartzbaum 1973). In this regard, it is interesting that the nigrostriatal system and the pallidum appear to share a common function in the lateralized control of sensorimotor behaviour/

behaviour - notably forelimb use (see Levine and Schwartzbaum, 1973; Marshall et al., 1974; also Figure 9). Furthermore, it has been shown in this thesis that a unilateral nigrostriatal lesion produces in the same animals an enhancement of food spillage (Table IV) and an incapacitation of the contralateral forelimb (Figure 6). There is little doubt, therefore, that in the consideration of neural systems known to be important in the control of sensorimotor function an abnormally high rate of food spillage may be regarded as an index of sensorimotor dysfunction.

As proposed elsewhere (6:4(iii)), the depression of food spillage by haloperidol may be related to the therapeutic action of this drug in the treatment of psychotic disorders. It may just be that haloperidol-induced reduction of the rate of food spillage represents an enhancement of the animal's control over its actions - an effect probably mediated through the reduction of "noise" in central DA synapses.

Another suggestion which emerges from the finding that haloperidol treatment did not increase food spillage like nigrostriatal damage (compare Table IV with Tables XIV and XVIII) is that the pharmacological blockade of DA receptors is an event different from the destruction of the nigrostriatal DA pathway in its effect on the transmission of neural impulses in the control of sensorimotor function. Whereas nigrostriatal damage disrupts this kind of neural transmission, haloperidol treatment does not, whatever other effects the two experimental procedures produce identically. This viewpoint is supported by the "converse" finding in another experiment that apomorphine stimulation of the post-synaptic DA receptors does not restore the capacity to use a forelimb incapacitated by nigrostriatal damage (see Figure 16).

8:6 THE NIGROSTRIATAL DOPAMINE SYSTEM AND MOTIVATION

Motivation, which may be described as a goal-directed state of arousal, is a cardinal feature of an organism's quest to satisfy its survival-related needs. Motivation, however, rather than being an end in itself, is a means to an end. In other words, it is not a survival-related need - and probably not an ultimate homeostatic objective in life. This latter proposal (in parenthesis) is implied in the hypothesis put forward somewhere else in this discussion to explain the apparent involvement of the nigrostriatal DA system in the control of body weight and food intake (8:4). It appears from the relevant experiment (see Chapter 3) (a) that permanently cutting off the nigro-striatal DA supply, even on one side of the brain, automatically produces in an animal a lowering of the homeostatic target-pattern in body weight, and (b) that this effect on body weight regulation determines the amounts of food required and also the need (i.e. motivation) to procure such amounts under conditions of unlimited food availability or of restricted access to supplies.

If this interpretation of the experimental results appertaining to nigrostriatal dopaminergic control of motivation is correct, it is obvious that the control is exerted by an indirect action.

Two complementary modes of action seem to be involved in the nigrostriatal dopaminergic control of the motivation for food. One is arousal. In this regard it is important to recall (a) that animals sustaining bilateral nigrostriatal damage become akinetic (Fibiger, Zis and McGeer, 1973a; 1973b; Oltmans and Harvey, 1972, Ungerstedt, 1971a; Zigmond and Stricker, 1972) as well as displaying a variety of deficits relating to ingestive behaviour, and (b) that it has been proposed that the/

the real deficit suffered by animals with bilateral nigrostriatal lesions is a deficit in the arousal component of behaviour (Stricker and Zigmond, 1976). It should be recalled furthermore that drugs which increase activity at catecholamine synapses enhance electrocortical activation and behavioural responsiveness (Jouvet, 1972). The other process whereby the nigrostriatal DA system appears to influence the motivation for food is the action of DA on striatal intrinsic neurons. DA is believed to exert an inhibitory action on a large number of neurons in the striatum (Bloom et a., 1965; Connor, 1970; McLennan and York, 1967). The results from one of the experiments presented in this thesis show that a discrete ablation of striatal intrinsic neuronal perikarya in one hemisphere produces a facilitation of body weight increase (see Table XXIII) and eventually an enhancement of food intake also (Table XXIV). The results from another experiment show that prolonged treatment with haloperidol produces a certain amount of facilitation of body weight increase (see 6:4(ii)). It is suggested therefore, that there might be in the striatum a neuronal population which under normal conditions exercises an inhibitory control on body weight, and that under normal conditions this inhibitory control is limited by the depressant action of striatal DA on this neuronal population to produce the balance reflected in normal patterns of body weight increase. Thus if DA supply is cut off the weight depressant action of these striatal intrinsic neurons appears to be accentuated. On the other hand, if these neurons are ablated, or if their effectiveness is reduced, say by the action of haloperidol, a facilitation of body weight occurs.

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The depression of food intake observed in connection with chronic haloperidol treatment (Tables XV and XXVII) probably reflects a deficit in arousal due to reduced activity in DA synapses (Jouvet, 1972), notably in the striatum. It appears that motivation, of which arousal is an inalienable component, provides a bridge between a physiologic set-point in body weight on one hand and food intake on the other. Although there appears to be a direct facilitation of body weight increase by chronic haloperidol treatment (or by a discrete ablation of striatal intrinsic neuronal perikarya, for that matter), body weight depends ultimately on food intake. Therefore, where a gap exists between the weight target and food intake, owing perhaps to a deficit in the arousal component of the motivational process, body weight eventually declines. This was observed in one of the haloperidol experiments reported in the present thesis (see Figure 20).

Unfortunately, the precise contribution of mesolimbic DA to motivation was not determined in the present project. Considering the model of Iversen (1977) in which it is proposed that the mesolimbic DA system mediates motivational arousal more directly than the nigrostriatal DA system it might be significant that all the animals displaying an impairment of the motivation for food following 6-OHDA microinjections into the MFB suffered a severe loss of mesolimbic ("limbic forebrain"), as well as striatal, DA. One way to test the possibility of mesolimbic involvement would be to administer 6-OHDA directly into the nucleus accumbens and see whether this treatment affects the motivation for food.

In the light of the results from the present project it can only be suggested that brain DA appears to be involved in the kind of motivation. The contribution of the nigrostriatal DA system might be made in two ways. Firstely, this system might contribute directly to arousal, so important in motivation, by activating the DA receptors in the striatum. Secondly,

it might indirectly elevate the physiological set-point for body weight by impairing a neuronal system which may be involved in the inhibitory control of body weight. It appears that an animal's body weight target determines in part its physiological need for food, while its state of arousal provides the drive to procure satisfaction in respect of that need. These two processes together manifest as the motivation for food.

8:7 THE NIGROSTRIATAL DOPAMINE SYSTEM AND SPACE-RELATED BEHAVIOUR

That experimentally produced asymmetry between the nigrostriatal

DA systems of the two hemispheres makes an animal rotate toward the less active of the two systems has been demonstrated by several authors (Anden et al., 1966; Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1970; Zimmerberg and Glick, 1975). In agreement with the results published by these authors are the observations presented in several parts of this thesis that a unilateral lesion of the nigrostriatal DA pathway (a) produces an enhancement of the number of rotations an animal performs during an operant behaviour session (see Figures 13 and 29), and (b) predisposes the animal to rotate only in the direction of the lesioned nigrostriatal DA pathway (see Figures 7d(ii), 13, 15c and 29).

In one of the experiments here presented unilateral postsynaptic disruption of the nigrostriatal DA system, achieved by lesioning the striatum on one side with kainic acid, also produced a certain amount of increase in rotational behaviour and some preference for the ipsiversive direction of circling (Figure 29). However, the rats with a kainate lesion of the striatum performed much fewer rotations than those with a 6-OHDA lesion of the MFB over an identical period of time (compare Figures 13 and 29). Moreover, a unilateral kainate lesion of the striatum permitted some rats to perform contraversive as well as ipsiversive rotations whereas all the rotations performed at an identical time after surgery (i.e. 1wk postoperatively) by animals sustaining a unilateral 6-OHDA lesion of the MFB were exclusively ipsiversive (compare Figures 13 and 29). An explanation for these differences between the effects of the two kinds of unilateral damage on rotational behaviour is not readily available. However, it is important that whereas successful 6-OHDA microinjection into the MFB completely destroys the nigrostriatal DA pathway and cuts off DA supply to the striatum (see/

(see Table IX, for example) without damaging non-catecholamine systems (Ungerstedt, 1968; 1971b) except for a small area of tissue necrosis at the site of injection (Butcher, 1975; Javoy, Soleto, Harbert and Agid, 1976), a kainate lesion of the striatum may and may not ablate all the DA postsynaptic receptor neurons, since a limited volume of the solution is used to prevent it from spreading outside the striatum. Thus greater nigrostriatal asymmetry is produced by a unilateral 6-OHDA lesion of the MFB than by a unilateral kainate lesion of the striatum; and it should not be very surprising that lesion effect on rotational behaviour is more pronounced following the former than following the latter surgical procedure.

As well as rotational behaviour, side preference in a T-maze has been reported to be related to asymmetry between the nigrostriatal DA systems of the two hemispheres (Rothman and Glick, 1976; Zimmerberg, 1975; Zimmerberg et al., 1974). In one of these studies (Rothman and Glick, 1976) a unilateral caudate lesion produced preference for the ipsilateral arm of the maze, and lesions localized in certain parts of the striatum were more effective than lesions placed in other parts of the same structure. Rothman and Glick concluded that reduced activity in the nigrostriatal DA system on the lesion side was responsible for the ipsilateral side preference displayed by those of their rats sustaining an effective unilateral caudate lesion. Their conclusion is confirmed by an experiment presented in this thesis (see Figure 14a), in which a unilateral 6-OHDA lesion of the nigrostriatal DA pathway on the side opposite to the preferred arm of a T-maze produced a dramatic reversal of side preferences.

Although the effect of a unilateral kainate lesion of the striatum

on/

on T-maze behaviour was not investigated in the present project, ~~there is little doubt~~ it seems likely that such a lesion will also produce an ipsilateral side preference, provided the DA postsynaptic receptor neurons in the striatum are decimated or completely ablated.

In the present project, neither a unilateral 6-OHDA lesion of the nigrostriatal DA pathway nor a unilateral kainate lesion of the striatum produced a preference for the ipsilateral lever in a two-lever operant behaviour situation (see Figures 12 and 28). The former surgical procedure produced no consistent effect on lever preference, and the latter procedure actually appears to have led to increased preference for the contralateral lever. These observations are at variance with the report by Glick and Jerussi (1974) that rats prefer the lever on the same side as the striatum with the lesser supply of DA when tested in a two-lever operant behaviour situation. The discrepancy between the present author's results on one hand and the results obtained by Glick and Jerussi on the other, regarding lever preference is difficult to explain, although there is the possibility that important differences exist between the operant behaviour boxes used. Anyway, the observation that a reversal of side preferences in a T-maze following a unilateral lesion of the nigrostriatal pathway is associated with increased goal rejections, particularly on the side less used prior to surgery (see Figures 14b(i) and 14b(ii)), may be relevant to the interpretation of the present author's results in respect of lever preference in a two-lever Skinner box. Thus goal preferences, as distinct from side preference, in a T-maze seems to represent a dimension of spatial behaviour which is not determined by asymmetry between the nigrostriatal systemsof the brain in the way that side preference is. The dimension of spatial behaviour represented by goal/

goal preference in a T-maze may be defined in terms of locating objects in space, and would include lever preference in a two-lever Skinner box. If this hypothesis is correct, it should not be surprising that a unilateral nigrostriatal pathway lesion failed to produce an ipsilateral lever preference in the present project.

The observation that a unilateral kainate lesion of the striatum produced a preference for the contralateral lever is even more difficult to explain. However, a hypothesis that may be worth considering is that the striatum contains neurons which are concerned with a kind of spatial preference based on the active location of objects in space. If such neurons exist in the striatum, the indication from the relevant experiment herein presented (see Figure 28) is that they function ipsilaterally; in other words, it appears that neurons intrinsic to the left striatum would be primarily concerned with the area of space to the left, whereas right striatal neurons would focus more on the right.

8:8 THE NIGROSTRIATAL DOPAMINE SYSTEM AND LEARNING

Unilateral nigrostriatal damage adversely affects the acquisition of an operant response through the elaboration of "compulsive" rotation (see 3:4(ii), 4:4(i)). This kind of disruption of learning seems to involve two distinct effects of the circling syndrome. Firstly, frequent circling appears to reduce the chances of an animal making the indispensable association between its action, e.g. lever pressing, and the availability of reward, e.g. food pellets. Secondly, forced circling seems to have a special disruptive effect, probably emotional, on behaviour in an operant situation (see 3:4(ii)). An impairment of the association stage in operant learning due to frequent and compulsive circling/

circling may therefore account for the failure of some lesioned animals to acquire an operant response in the learning experiments presented in this thesis (see 3:3(ii) and 4:3(C)(i)). It does not, however, explain the observation (3:3(ii)) that two lesioned animals appeared to have learned and then 24hrs later showed no signs of learning, under conditions identical to those in which control animals displayed a confirmation of the acquired response (see 2:2 and 3:3(ii)). It seems that there is indeed a fundamental and direct impairment of learning capacity following nigrostriatal damage and that this impairment may be in the consolidation stage.

The view that nigrostriatal damage impairs learning capacity directly is supported by the finding by Ranje and Ungerstedt (1977), that bilateral damage disrupts the capacity to learn a discrimination task. The nigrostriatal DA system may therefore be involved in learning in ways that are at the moment not known; and it may be worthwhile to address more research efforts to the investigation of the role of this system in various kinds of learning.

8:9 LESIONING WITH 6-HYDROXYDOPAMINE AND KAINIC ACID

In the studies employing 6-OHDA as a lesioning tool, microinjection of this neurotoxin into the MFB produced depletions not only of striatal DA but also of striatal NE and limbic forebrain DA (Tables VIII; IX, and X); in some cases limbic forebrain NE was also substantially reduced (see Table IX). The difference between the effects of 6-OHDA on limbic forebrain NE levels in different groups of rats is probably due to the fact that whereas most ss were pretreated with desipramine just before anaesthesia in the surgical procedure, that is about 30min before the actual/

actual microinjection of 6-OHDA, the other ss were pretreated 30min before anaesthesia. Two observations are obvious therefore from the results appertaining to the neurochemical effects of 6-OHDA microinjection into the MFB following pretreatment of the ss with desipramine. Firstly, pretreatment with desipramine does not appear to effectively counter the degenerative action of 6-OHDA on the NE system supplying the striatum, when the neurotoxin is applied to the MFB. This is probably because desipramine is not very effective in the striatum, in which there are more DA than NE axon terminals (Haggendal and Hamberger, 1969; Snyder, Green and Hendley, 1968). Secondly, pre-treatment with desipramine does appear to protect NE supplies to the limbic forebrain region provided it is given well in advance of the administration of 6-OHDA - better more than 30min in advance, than less!

The fact that 6-OHDA destroys not just one DA system but all DA and NE systems near the site of injection of the neurotoxin should be taken into account in experiments in which more than one catecholamine system might be involved in the functions being investigated. One way of dealing with the problem of limited specificity of action of the drug is to investigate the same functions over and over again using other techniques that will eventually, considered side by side with the 6-OHDA experiment, isolate the system or systems which are importantly involved in the functions. This remedy has been adopted in parts of the work presented in this thesis. For example, ingestive behaviour and body weight regulation, forelimb control, rotational behaviour and lever choice in a two-lever operant-behaviour box were investigated using, in separate experiments, a kainic acid lesion of the striatum and 6-OHDA microinjection into the MFB.

The/

The main value of the kainic acid technique in the work presented in this thesis lies in the fact that kainic acid as a lesioning tool is known to selectively destroy neuronal perikarya, sparing axon terminals and fibres of passage through the site of administration (Schwarcz and Coyle, 1977). Although striatal DA and NE levels were not determined in animals sustaining a kainic acid lesion of the striatum to confirm that catecholamine terminals supplying the striatum were intact, the results of assays in respect of limbic forebrain DA and NE showed that the fibre systems supplying these amines to the limbic forebrain region were not damaged to the extent that they had been following a 6-OHDA lesion of the MFB (compare Tables VIII and IX to Tables XVIII and XXX). The rather minor reductions observed in limbic forebrain levels of DA on the side with a kainate-lesioned striatum are probably due to mechanical damage from the injection cannula.

Several of the conclusions reached in the present enquiry have been made possible by the complementary use of different research techniques, notably the 6-OHDA and kainic acid lesioning procedures. The usefulness of this kind of approach cannot be over-emphasised, particularly in psychobiological investigations which do not permit a straightforward isolation of the neural systems of interest.

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APPENDIX A

Food intake (in grams) by rats with a unilateral 6-OHDA lesion of the nigrostriatal DA pathway vis-a-vis partially lesioned and unlesioned control ss. The asterisks indicate partially lesioned control ss.

Periods	Days	Experimental Group of Ss								
		A	B	C	D	E	F	G	H	Means±SD
	1	18.3	19.0	19.5	18.4	18.0	20.0	21.15	19.8	19±1
	2	18.0	21.3	18.3	16.7	16.0	19.9	30.0	20.2	20±4
Immediate	3	22.0	21.7	23.2	20.3	23.3	21.0	22.7	18.5	22±2
Preoperative	4	22.5	20.7	21.0	20.8	21.0	23.0	23.0	24.1	22±1
Week	5	21.5	22.5	23.4	18.5	23.6	20.7	21.5	16.8	21±2
	6	22.7	22.0	22.1	20.0	24.0	24.3	22.6	20.8	22±1
	7	23.7	22.0	21.3	21.0	25.0	25.0	26.5	21.2	23±2
	Totals	148.7	149.2	148.8	135.7	150.9	153.9	167.45	141.4	150±9
	1	7.6	2.9	4.9	11.4	11.5	4.2	5.7	19.9	9±6
	2	15.5	5.2	16.7	9.1	9.6	14.2	8.4	19.0	12±5
1st	3	18.4	14.0	17.9	16.7	15.5	17.5	13.3	37.0	19±8
Postoperative	4	18.1	14.7	17.1	16.0	14.0	16.7	9.4	20.9	16±3
Week	5	17.2	17.7	18.5	17.0	14.2	19.1	17.6	21.7	18±2
	6	19.3	19.8	18.2	17.8	18.4	15.6	18.7	23.7	19±2
	7	19.7	19.8	21.1	19.4	17.0	14.4	17.7	26.7	19±4
	Totals	115.8	94.1	114.4	107.4	100.2	101.7	90.8	168.9	112±25
	1	19.8	18.5	23.4	20.8	20.5	19.4	20.2	24.5	21±2
	2	21.7	21.0	24.6	20.0	18.0	19.7	21.1	20.1	21±2
2nd	3	20.5	19.2	23.3	21.8	21.5	19.3	16.1	27.2	21±3
Postoperative	4	22.9	19.4	25.2	20.8	20.5	23.6	21.5	25.5	22±2
Week	5	21.3	20.4	23.7	20.4	12.0	22.8	22.1	23.7	21±4
	6	18.1	19.6	24.2	18.6	17.0	23.6	22.9	25.4	21±3
	7	20.9	20.0	24.2	20.1	18.3	21.7	23.2	30.1	22±4
	Totals	145.2	138.1	168.6	142.5	127.8	150.1	147.1	176.5	149±16

Contd./

Periods	Days	Experimental Group of Ss								
		A	B	C	D	E	F	G	H	Means±SD
24hrs of Feeding following a period of Food Deprivation		26.7	29.1	30.9	27.1	28.8	28.9	21.1	30.0	28±3
	1	26.7		26.05	23.1		29.3	28.3		27±2
	2	24.3		25.3	26.3		29.75	26.6		26±2
14th	3	21.65		23.35	22.3		24.45	18.1		22±2
Postoperative	4	22.9		26.8	23.75		28.05	19.2		24±3
Week	5	23.15		25.3	23.5		29.7	25.6		25±3
	6	21.65		23.5	27.4		26.95	24.05		25±2
	7	22.85		23.7	20.7		24.7	21.0		23±2
	Totals	163.2		174.0	167.05		192.9	162.85		172±13

Periods	Days	Control Group of Ss									
		A*	B*	C*	D	E	F	G	H	I	Mean±SD
	1	21.5	20.4	19.2	19.5	20.0	18.5	21.0	18.9	19.1	20±1
	2	22.7	29.3	19.1	19.3	19.2	21.8	21.5	17.4	22.7	21±3
Immediate	3	23.5	21.5	22.0	20.3	17.3	21.6	19.4	17.3	19.1	20±2
Preoperative	4	22.0	20.4	22.4	23.0	19.3	25.0	21.5	21.8	23.7	22±2
Week	5	21.0	21.3	22.5	16.9	17.7	17.9	17.8	16.0	16.3	19±2
	6	23.3	24.7	24.3	22.5	23.2	22.4	21.5	23.7	23.5	23±1
	7	22.1	25.7	24.3	22.1	20.1	23.5	19.4	17.5	21.6	22±3
	Totals	156.1	163.3	153.8	143.6	136.8	150.7	142.1	132.6	146.0	147±10
	1	16.4	19.3	14.0	21.1	17.8	21.4	18.1	17.2	17.5	18±2
	2	21.7	27.0	23.1	39.1	27.0	30.0	31.1	29.0	31.7	29±5
1st	3	26.9	26.1	25.1	43.1	39.4	39.9	35.8	43.1	38.9	35±7
Postoperative	4	23.6	26.6	24.2	25.5	25.1	26.3	24.2	24.8	17.1	24±3
Week	5	24.1	30.9	25.1	22.9	24.6	23.0	19.1	22.0	22.9	24±3
	6	26.8	27.2	25.3	26.3	26.2	25.1	24.8	25.1	23.6	26±1
	7	27.2	30.2	24.8	22.9	25.8	28.6	23.1	24.9	22.7	26±3
	Totals	166.7	187.3	161.6	161.8	158.9	164.3	145.1	157.1	142.7	161±13
	1	26.2	29.7	25.6	26.1	29.1	27.0	24.5	26.5	24.3	27±2
	2	30.2	29.5	23.6	26.8	23.9	24.9	24.9	23.9	22.7	26±3
2nd	3	28.8	29.8	25.7	25.6	31.5	31.7	29.1	26.9	26.8	28±2
Postoperative	4	31.2	31.6	27.2	27.5	28.6	27.6	27.2	26.1	27.7	28±2
Week	5	28.8	27	26.3	25.4	27.0	29.7	25.8	23.9	26.2	27±2
	6	29.6	29.2	26.0	26.0	30.1	30.7	27.1	28.6	28.1	28±2
	7	30.6	30.5	25.5	30.0	33.7	39	30.5	30.2	31.8	31±4
	Totals	205.4	207.3	179.9	187.4	203.9	210.6	189.1	186.1	187.6	195±11

Contd./

Periods	Days	Control Group of Ss									
		A*	B*	C*	D	E	F	G	H	I	Mean±SD
24hrs of Feeding following a Period of Food Deprivation		35.8	37.7	33.2	34.1	34.7	38.6	32.3	33.3	25.9	35±2
14th Postoperative Week	1				25.5	29.35	34.55	32.8	31.55	33.4	31±4
	2				26.75	31.8	35.35	32.0	29.4	28.45	31±3
	3				24.25	27.3	31.8	27.7	25.15	30.55	27±3
	4				24.8	31.85	35.4	31.75	29.15	23.85	29±4
	5				25.85	30.3	33.15	28.0	24.5	29.7	29±3
	6				23.5	27.85	28.2	28.75	28.6	29.45	28±2
	7				21.55	27.75	32.5	26.0	27.95	26.1	27±4
	Totals				172.2	206.2	230.95	207.0	196.3	201.5	202±19

APPENDIX B

Quantity of food (in grams) bitten off in the process of feeding by rats with a unilateral 6-OHDA lesion of the nigrostriatal DA pathway vis-a-vis partially lesioned and unlesioned controls. The asterisks refer to partially lesioned control ss.

Periods	Days	Experimental Group of Ss								
		A	B	C	D	E	F	G	H	Mean±SD
	1	20.3	22.0	21.5	21.0	20.5	22.0	24.5	21.8	22±1
	2	21.6	25.3	21.3	19.0	19.0	24.5	34.0	25.4	24±5
Immediate	3	26.0	26.0	26.5	23.6	26.3	26.0	27.0	20.8	25±2
Preoperative	4	26.5	25.0	24.0	24.3	23.6	27.0	27.0	27.1	26±1
Week	5	24.5	26.5	27.0	21.5	26.6	24.0	25.0	19.3	24±3
	6	26.0	26.0	25.6	24.5	26.6	26.6	26.6	25.0	26±1
	7	26.0	26.0	24.3	25.0	28.0	29.0	31.0	25.0	27±2
	Totals	170.9	176.8	171.2	158.9	170.6	179.1	195.1	164.4	173±11
	1	12.0	3.3	5.6	14.3	17.5	5.5	10.7	27.5	12±8
	2	20.5	10.2	19.0	12.4	16.2	22.2	11.9	35.0	18±8
1st	3	25.6	21.0	22.5	21.7	20.5	26.8	18.4	55.0	26±12
Postoperative	4	25.7	26.4	23.1	22.0	20.1	30.2	16.6	35.7	25±6
Week	5	24.5	30.5	26.8	22.6	19.6	44.1	32.6	34.7	29±8
	6	26.7	33.9	21.7	23.3	28.4	40.9	30.5	35.6	30±6
	7	30.6	36.9	28.0	25.0	26.1	48.1	29.6	39.0	33±8
	Totals	165.6	162.2	146.7	141.3	148.4	217.8	150.3	262.5	174±43
	1	30.0	29.8	29.0	27.8	30.9	49.4	33.0	38.0	33±7
	2	31.0	43.3	32.9	26.4	24.0	38.9	37.4	32.0	33±6
2nd	3	27.8	35.2	31.0	29.0	28.5	37.0	29.0	43.0	33±5
Postoperative	4	30.9	33.4	31.6	26.3	26.0	42.8	35.5	39.8	33±6
Week	5	29.9	36.0	31.5	27.0	14.0	39.8	34.3	35.1	31±8
	6	26.9	36.0	31.2	24.7	20.5	42.8	32.3	38.3	32±7
	7	28.1	34.9	31.6	25.7	23.3	38.7	32.5	46.3	33±7
	Totals	204.6	248.6	218.8	186.9	167.2	289.4	234.0	272.5	228±42

Contd./

Periods	Days	Experimental Group of Ss								
		A	B	C	D	E	F	G	H	Mean$^{+}_{-}$SD
24hrs of Feeding following a Period of Food Deprivation		36.7	55.6	39.4	34.0	38.7	55.9	43.8	41.0	43$^{+}_{-}$8
	1	37.9		33.8	40.1		39.1	38.1		38$^{+}_{-}$2
	2	31.85		33.2	31.3		39.05	33.6		34$^{+}_{-}$3
14th	3	28.95		27.85	26.5		34.1	24.1		28$^{+}_{-}$4
Postoperative	4	33.3		32.1	29.55		36.75	25.8		32$^{+}_{-}$4
Week	5	31.6		31.2	27.0		42.0	35.7		34$^{+}_{-}$6
	6	32.7		31.0	34.0		36.85	29.65		33$^{+}_{-}$3
	7	31.95		31.2	25.25		34.15	26.5		30$^{+}_{-}$4
	Totals	228.25		220.35	213.7		262.0	213.45		228$^{+}_{-}$18

Periods	Days	Control Group of Ss									
		A*	B*	C*	D	E	F	G	H	I	Mean±SD
Immediate Preoperative Week	1	25.5	25.0	22.5	22.1	22.7	20.3	24.2	21.0	24.1	23±2
	2	26.0	34.3	23.6	21.7	21.8	23.8	25.3	19.8	27.7	25±4
	3	27.0	28.5	26.0	23.3	21.2	24.0	22.6	19.6	24.1	24±3
	4	26.0	28.0	26.0	26.0	23.6	28.0	24.1	24.8	29.0	26±2
	5	25.0	26.6	26.0	19.0	21.7	20.3	20.2	18.0	20.1	22±3
	6	27.3	31.0	28.3	25.0	27.8	25.4	24.2	27.3	27.7	27±2
	7	25.6	30.0	28.3	25.1	25.0	25.6	21.9	20.1	26.1	25±3
	Totals	182.4	203.4	180.7	162.2	163.8	167.4	162.5	150.6	178.8	172±16
1st Postoperative Week	1	21.0	22.3	18.0	24.0	21.7	25.6	23.0	22.0	21.0	22±2
	2	26.0	31.0	27.4	45.0	35.0	39.2	40.1	38.0	38.7	36±6
	3	31.3	30.1	30.1	49.0	47.9	48.2	44.6	52.3	45.9	42±9
	4	28.1	31.2	29.2	28.5	30.4	31.4	30.5	29.0	20.0	29±3
	5	28.1	35.8	29.2	25.8	31.0	28.4	24.0	26.0	27.0	28±3
	6	21.8	31.7	29.5	29.8	33.0	32.1	29.8	30.5	28.6	31±1
	7	32.1	36.0	28.8	26.1	33.7	34.8	28.0	29.1	27.4	31±4
	Totals	198.4	218.1	192.2	228.2	232.7	239.7	220.0	226.9	208.6	218±16
2nd Postoperative Week	1	30.8	34.0	29.3	30.0	36.5	32.9	30.1	31.0	29.2	32±2
	2	35.2	34.5	27.8	30.2	28.0	30.9	30.9	30.4	26.8	31±3
	3	32.8	34.4	30.5	29.0	37.8	38.0	35.0	32.9	33.0	34±3
	4	36.0	36.3	31.9	31.0	35.0	32.7	33.8	31.7	33.0	33±2
	5	33.5	31.2	30.6	30.1	33.0	35.8	31.9	28.0	31.8	32±2
	6	33.8	33.9	30.0	29.9	36.1	26.8	34.0	33.6	33.9	34±2
	7	34.7	35.5	29.3	35.0	41.0	46.4	39.5	36.0	39.6	37±5
	Totals	236.8	239.8	209.4	215.2	247.1	253.5	235.2	223.6	227.3	232±14

Contd./

Periods	Days	Control Group of Ss									
		A*	B*	C*	D	E	F	G	H	I	Mean±SD
24hrs of Feeding following a Period of Food Deprivation.		40.8	43.5	38.4	38.4	41.0	45.6	38.3	39.6	44.6	41±3
	1				29.1	35.05	40.0	40.75	37.0	40.1	37±4
	2				30.05	37.3	42.3	38.0	34.2	35.15	36±4
14th	3				27.75	31.3	36.7	32.5	29.05	36.1	32±4
Postoperative	4				28.0	36.15	41.0	36.75	33.1	28.75	34±5
Week	5				29.0	35.4	39.45	33.65	27.0	35.55	33±5
	6				26.0	32.85	33.1	33.75	33.5	35.75	32±3
	7				24.8	32.0	38.5	30.7	32.05	31.9	32±4
	Totals				194.7	240.04	271.05	246.1	225.9	243.3	237±25

APPENDIX C

Food intake (in grams) by rats chronically treated with a moderately high dose of haloperidol (1mg/kg/day for 25 days) and by saline-treated controls.

Periods	Days	Experimental Group of Ss						
		A	B	C	D	E	F	Mean±SD
Pretreatment Days 5 - 0	1	24.1	24.8	21.6	20.7	20.9	22.4	22±2
	2	25.6	28.1	23.9	22.7	22.3	20.5	24±3
	3	21.1	27.0	22.1	20.5	23.6	22.9	23±2
	4	24.1	28.1	23.1	23.1	22.4	24.9	24±2
	5	20.2	32.5	23.7	24.2	26.0	22.7	25±4
	Totals	115.1	140.5	114.4	111.2	115.2	113.4	118±11
Treatment Days 0 - 5	1	11.6	28.2	24.4	23.5	25.3	2.5	19±10
	2	16.4	26.2	24.1	18.7	23.0	3.3	19±8
	3	19.2	29.6	23.8	21.0	23.2	20.1	23±4
	4	20.2	25.0	25.9	22.7	26.1	25.0	24±2
	5	23.3	27.7	23.4	22.3	21.9	24.7	24±2
	Totals	90.7	109.77	121.6	108.2	119.5	75.6	104±18
Treatment Days 5 - 10	1	23.0	27.6	26.4	24.6	26.3	28.1	26±2
	2	25.8	26.8	24.5	22.2	24.4	25.8	25±2
	3	25.2	27.3	23.5	24.2	24.2	25.8	25±1
	4	25.5	26.2	22.0	26.7	24.7	23.1	25±2
	5	25.9	24.7	21.6	20.3	23.8	22.7	23±2
	Totals	125.4	132.6	118.0	118.0	123.4	125.5	124±5
Treatment Days 10 - 15	1	26.0	26.8	20.8	21.3	22.7	22.6	23±2
	2	23.1	25.3	22.05	20.7	22.0	22.6	23±2
	3	29.9	24.9	23.0	21.1	21.1	22.5	24±3
	4	24.1	27.6	22.0	23.9	24.1	24.3	24±2
	5	22.8	24.4	21.0	22.3	19.6	23.1	22±2
	Totals	125.9	129.0	108.85	109.3	109.5	115.1	116±9
1hr of Feeding following a Period of Food Deprivation.		1.0	1.4	3.35	0.0	1.3	1.0	1±1

Contd./

Periods	Days	Experimental Group of Ss						
		A	B	C	D	E	F	Mean$\pm$SD
24hrs of Feeding following a Period of Food Deprivation		28.0	32.1	29.4	25.2	24.7	32.1	29$\pm$3
Treatment Days 17 - 20	1	22.7	25.9	22.05	18.7	17.5	20.2	21$\pm$3
	2	21.0	27.5	24.3	19.7	18.6	28.0	23$\pm$4
	3	26.3	25.7	22.4	24.85	22.5	26.55	25$\pm$2
	Totals	70.0	79.1	68.75	63.25	58.6	74.75	69$\pm$7
Treatment Days 20 - 25	1	24.05	26.3	25.05	23.3	21.85	27.65	25$\pm$2
	2	27.1	27.5	25.3	25.8	24.9	31.0	27$\pm$2
	3	24.75	29.3	25.0	22.9	18.2	23.9	24$\pm$4
	4	21.2	32.1	27.5	29.45	15.3	24.2	25$\pm$6
	5	22.7	28.8	26.3	27.8	16.8	30.7	26$\pm$5
	Totals	119.8	144.05	129.15	129.25	97.05	137.45	126$\pm$16
Posttreatment Days 0 - 5	1	27.0	30.4	24.2	23.05	19.9	27.6	25$\pm$4
	2	23.85	24.05	25.5	23.65	14.5	20.75	22$\pm$4
	3	27.55	28.1	21.95	24.65	26.7	26.5	26$\pm$2
	4	32.2	31.7	28.2	23.05	24.15	23.45	27$\pm$4
	5	28.25	31.5	28.4	26.0	28.45	23.85	28$\pm$3
	Totals	138.85	145.75	128.25	120.4	113.7	122.15	128$\pm$12

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean±SD
Pretreatment Days 5 - 0	1	22.1	21.7	29.0	24.6	24.0	21.7	24±3
	2	22.9	22.6	31.4	23.1	23.0	20.6	24±4
	3	17.5	23.8	30.5	22.7	21.8	20.9	23±4
	4	24.8	26.4	29.3	26.3	23.2	21.5	25±3
	5	18.4	25.0	25.2	23.8	23.7	17.1	22±4
	Totals	105.7	119.5	145.4	120.5	115.7	101.8	118±15
Treatment Days 0 - 5	1	16.1	24.6	23.2	20.0	24.5	18.0	21±4
	2	9.8	25.3	26.5	15.9	24.5	19.0	20±7
	3	21.7	24.5	25.9	23.5	25.6	18.8	23±3
	4	20.8	19.4	23.2	20.6	27.7	17.6	22±4
	5	21.4	24.5	25.5	19.6	26.8	23.0	23±3
	Totals	89.8	118.3	124.3	99.6	129.1	96.4	110±16
Treatment Days 5 - 10	1	24.0	24.9	26.4	23.8	25.3	20.2	24±3
	2	23.3	24.8	28.0	24.2	27.9	22.5	25±2
	3	24.8	24.9	26.4	22.5	27.3	22.6	25±2
	4	25.6	22.8	26.2	28.4	27.8	25.4	26±2
	5	24.2	23.4	26.1	24.6	24.2	22.7	24±1
	Totals	121.9	120.8	133.1	123.5	.3215	113.4	124±8
Treatment Days 10 - 15	1	24.3	26.0	27.9	27.2	30.7	25.3	27±2
	2	25.3	22.7	14.9	26.8	23.4	23.4	23±4
	3	26.7	24.5	26.8	28.5	31.4	26.2	27±2
	4	25.8	24.6	25.6	27.2	27.6	21.2	25±2
	5	23.9	23.3	26.1	26.0	28.8	23.6	25±2
	Totals	126.0	121.1	121.3	135.7	141.9	119.7	128±9
1hr of Feeding following a Period of Food Deprivation		10.0	4.6	2.9	7.55	7.2	9.55	7±3

Contd./

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean$\pm$SD
24hrs of Feeding following a Period of Food Deprivation		33.3	30.3	29.5	34.4	32.9	33.9	32 ± 2
Treatment Days 17 - 20	1	24.8	25.15	26.95	24.55	28.5	24.25	26 ± 2
	2	24.8	24.6	28.0	25.6	29.0	23.6	26 ± 2
	3	29.6	27.6	29.35	27.65	30.4	23.1	28 ± 3
	Totals	79.2	77.35	84.3	77.8	87.9	70.95	80 ± 6
Treatment Days 20 - 25	1	27.9	24.85	28.65	29.8	31.7	25.35	28 ± 3
	2	27.0	26.7	29.3	30.1	30.5	29.4	29 ± 2
	3	32.65	27.05	30.85	33.7	35.7	28.15	31 ± 3
	4	26.6	29.25	28.7	30.9	33.1	26.65	29 ± 3
	5	32.2	27.0	32.9	32.55	30.95	24.35	30 ± 4
	Totals	146.35	134.85	150.4	157.05	161.95	133.9	147 ± 11
Posttreatment Days 0 - 5	1	28.15	29.0	29.85	32.0	32.3	25.8	30 ± 2
	2	30.1	26.25	30.05	31.05	32.4	24.95	29 ± 3
	3	26.7	26.9	29.5	31.45	32.9	24.6	29 ± 3
	4	33.4	30.15	30.95	31.5	35.5	28.1	32 ± 3
	5	28.1	31.8	32.75	33.6	38.2	29.95	23 ± 3
	Totals	146.45	144.1	153.1	159.6	171.3	133.4	151 ± 13

APPENDIX D

Food intake (in grams) by rats chronically treated with a very high dose of haloperidol (10mg/kg/day for 3 days) and by saline-treated controls.

Periods	Days	Experimental Group of Ss						
		A	B	C	D	E	F	Mean $\pm$SD
Pretreatment Days 3 - 0	1	18.7	21.45	22.35	19.3	23.9	19.4	21 ± 2
	2	17.25	20.15	20.1	20.7	26.0	18.3	20 ± 3
	3	23.15	21.95	21.4	23.45	23.15	20.3	22 ± 1
	Totals	59.1	63.55	63.85	62.45	73.05	58.0	63 ± 5
Treatment Days 0 - 3	1	16.7	15.15	16.65	15.5	16.35	15.95	16 ± 1
	2	17.55	19.05	17.75	15.3	17.0	17.6	17 ± 1
	3	20.95	21.5	22.2	21.3	22.8	18.15	21 ± 2
	Totals	55.2	55.7	56.6	52.1	56.15	51.7	55 ± 2
Posttreatment Days 0 - 3	1	17.5	21.5	19.05	19.0	19.2	18.55	19 ± 1
	2	22.05	20.75	22.95	21.85	24.7	21.85	22 ± 1
	3	23.0	22.2	26.0	22.05	26.1	22.5	24 ± 2
	Totals	63.55	64.45	68.0	62.9	70.0	62.9	65 ± 3

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean±SD
Pretreatment Days 3 - 0	1	16.7	18.0	18.65	21.65	18.65	19.0	19±2
	2	21.5	22.6	22.1	22.15	20.7	21.5	22±1
	3	19.75	20.05	20.2	20.75	22.05	21.8	21±1
	Totals	57.95	60.65	60.95	64.55	61.4	62.3	61±2
Treatment Days 0 - 3	1	20.8	22.6	21.7	23.55	20.55	25.95	23±2
	2	18.7	20.55	22.4	22.7	21.9	21.6	21±2
	3	23.55	25.1	20.7	23.15	28.4	24.8	24±3
	Totals	63.05	68.25	64.8	69.4	70.85	72.35	68±4
Post treatment Days 0 - 3	1	20.7	23.0	21.85	22.1	19.45	23.5	22±1
	2	21.75	20.75	23.25	22.05	25.5	27.1	23±2
	3	22.9	24.3	23.75	24.6	27.3	26.65	25±2
	Totals	65.35	68.05	68.85	68.75	72.25	77.25	70±4

APPENDIX E

Water intake (in millilitres) by rats chronically treated with a very high dose of haloperidol (10mg/kg/day for 3 days) and by saline-treated controls.

Periods	Days	Experimental Group of Ss						
		A	B	C	D	E	F	Mean ±SD
Pretreatment Days 3 - 0	1	30.0	26.0	25.0	36.0	22.0	24.0	27±5
	2	28.5	24.0	23.0	27.5	28.0	24.0	26±2
	3	38.0	27.0	28.0	25.0	29.0	29.0	29±5
	Totals	96.5	77.0	76.0	88.5	79.0	77.0	82±8
Treatment Days 0 - 3	1	35.0	20.0	20.0	20.0	25.0	22.0	24±6
	2	20.0	18.0	21.0	18.0	30.0	29.0	23±5
	3	39.0	26.0	31.0	27.0	24.0	32.0	30±5
	Totals	94.0	64.0	72.0	65.0	79.0	83.0	76±12
Post treatment Days 0 - 3	1	31.0	27.0	27.0	28.0	28.0	29.0	28±2
	2	40.0	26.0	26.0	27.0	27.0	25.5	29±6
	3	38.0	27.0	29.0	27.5	29.0	25.0	29±5
	Totals	109.0	80.0	82.0	82.5	84.0	79.5	86±11

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean $\pm$SD
Pretreatment Days 3 - 0	1	32.0	25.0	29.0	24.0	29.0	28.0	28 ± 3
	2	32.0	34.0	30.0	30.0	29.0	30.0	31 ± 2
	3	30.0	29.0	25.0	25.5	24.0	25.0	26 ± 2
	Totals	94.0	88.0	84.0	79.5	82.0	83.0	85 ± 5
Treatment Days 0 - 3	1	30.0	35.0	30.0	32.0	30.0	32.0	32 ± 2
	2	28.0	27.0	25.0	24.0	25.0	31.0	27 ± 3
	3	36.0	39.0	30.5	39.0	38.0	34.0	36 ± 3
	Totals	94.0	101.0	85.5	95.0	93.0	97.0	94 ± 5
Post treatment Days 0 - 3	1	27.5	27.0	28.5	26.0	27.0	26.0	27 ± 1
	2	34.5	28.5	27.5	28.5	30.0	31.5	30 ± 3
	3	38.0	36.0	30.0	30.0	35.0	31.0	33 ± 3
	Totals	100.0	91.5	86.0	84.5	92.0	88.5	90 ± 6

APPENDIX F

Food intake (in grams) by rats with a unilateral kainate-induced striatal lesion and by vehicle-injected controls.

Periods	Days	Experimental Group of Ss							
		A	B	C	D	E	F	G	Mean±SD
Immediate Preoperative Week	1	17.95	20.04	16.75	19.0	18.56	19.49	16.64	19±1
	2	18.27	19.81	19.62	20.01	19.93	20.0	20.48	20±1
	3	19.23	21.46	19.68	21.44	18.4	23.04	21.57	21±2
	4	21.07	21.95	19.52	20.55	18.99	20.76	21.49	20±1
	5	21.05	22.4	23.76	24.62	19.99	23.8	24.4	23±2
	6	20.48	21.95	20.7	21.6	21.3	19.0	22.33	21±1
	7	21.69	21.72	21.34	24.99	19.24	21.57	25.04	22±2
	Totals	139.74	149.33	141.37	152.21	136.41	146.94	151.95	144±6
1st Postoperative Week	1	0.0	0.0	0.28	0.0	0.2	0.0	0.0	0±0
	2	6.4	0.0	0.6	7.54	10.91	3.63	5.47	5±4
	3	24.68	0.5	8.18	23.34	22.17	17.22	5.6	16±10
	4	23.48	6.94	10.2	21.76	18.65	14.72	9.88	16±7
	5	21.15	14.9	13.54	23.86	22.54	22.03	12.77	20±4
	6	23.3	18.98	15.13	24.68	22.78	22.23	16.87	21±4
	7	23.98	22.61	18.89	21.6	27.81	25.96	20.38	23±3
	Totals	122.99	63.93	66.82	122.78	125.06	105.79	70.97	101±29
2nd Postoperative Week	1	22.57	26.08	26.65	26.92	25.86	26.8	21.62	25±3
	2	28.27	28.0	23.5	26.08	25.2	25.08	21.17	26±2
	3	26.99	28.84	25.5	27.43	23.79	27.4	24.33	27±2
	4	28.98	28.62	27.67	28.16	26.71	27.05	26.1	28±1
	5	29.94	28.48	27.91	28.42	26.76	29.54	27.14	29±1
	6	29.63	27.47	27.17	27.76	26.81	29.51	25.18	28±1
	7	31.7	29.8	25.49	29.72	30.25	28.36	26.5	29±2
	Totals	198.08	197.29	177.89	194.49	185.38	193.74	172.04	191±8

Contd./

Period	Days	Experimental Group of Ss							
		A	B	C	D	E	F	G	Mean$\pm$SD
24hrs of Feeding fcllowing a Period of Food Deprivation		38.54	32.38	30.06	33.63	33.89	31.99	32.86	33$\pm$3
During 24hrs of Water Deprivation		17.28	17.35	13.84	15.85	16.93	17.12	15.3	16$\pm$1
24hrs of Feeding following a Period of Water Deprivation		35.44	33.43	27.68	29.9	29.79	32.79	29.72	32$\pm$3

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean±SD
	1	18.42	17.08	20.33	18.5	17.58	23.07	19±2
	2	20.2	17.17	22.85	20.43	18.8	25.02	21±3
Immediate	3	19.89	18.77	22.79	17.92	19.5	23.31	20±2
Preoperative	4	22.07	20.43	21.36	22.36	23.02	25.55	22±2
Week	5	21.07	17.36	20.99	20.73	21.53	25.31	21±3
	6	19.33	17.48	21.2	20.35	22.98	25.7	21±3
	7	19.25	19.71	20.8	19.82	23.67	26.78	22±3
	Totals	140.23	128.0	150.32	140.11	147.08	174.74	147±15
	1	5.93	8.72	6.16	8.56	13.0	13.92	9±3
	2	13.54	19.76	15.86	20.26	20.18	22.5	19±3
1st	3	18.76	21.82	23.66	26.98	25.79	24.04	24±3
Postoperative	4	18.55	21.91	25.7	23.9	24.01	26.68	23±3
Week	5	23.04	22.59	28.07	26.29	28.84	27.73	26±2
	6	22.6	23.65	22.03	25.57	22.87	26.40	24±2
	7	23.87	24.71	29.29	27.18	17.6	32.62	26±5
	Totals	25.29	143.16	150.77	158.74	152.29	173.95	151±16
	1	24.92	23.3	30.0	27.62	28.42	29.86	27±3
	2	27.2	24.15	31.87	28.22	25.88	33.2	28±3
2nd	3	22.24	25.2	29.62	27.68	26.65	32.08	27±3
Postoperative	4	25.45	25.0	29.55	27.98	24.35	30.93	27±3
Week	5	25.61	24.85	28.23	26.16	25.33	32.0	27±3
	6	24.5	24.88	28.56	27.36	26.75	32.5	27±3
	7	25.8	25.78	30.93	26.03	27.1	33.9	28±3
	Totals	175.72	173.16	208.76	191.05	184.48	224.47	193±20

Contd./

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean±SD
24hrs of Feeding following a Period of Food Deprivation		35.46	32.58	35.03	37.73	33.23	42.36	36±4
During 24hrs of Water Deprivation		12.0	14.09	16.64	15.7	15.91	20.48	16±3
24hrs of Feeding following a Period of Water Deprivation		28.31	30.82	38.07	30.19	32.28	35.99	33±4

APPENDIX G

Water intake (in millilitres) by rats with a unilateral kainate-induced striatal lesion and by vehicle-injected controls.

Periods	Days	Experimental Group of Ss							
		A	B	C	D	E	F	G	Mean±SD
Immediate Preoperative Week	1	34.0	26.0	24.5	24.0	33.0	31.0	24.0	29±4
	2	33.0	27.5	28.0	30.0	26.5	32.0	28.5	31±3
	3	31.0	25.5	30.0	44.0	43.5	42.5	35.0	36±8
	4	32.0	26.5	27.0	36.0	37.0	35.0	34.0	32±5
	5	35.5	25.0	31.5	35.0	36.0	34.0	35.0	33±4
	6	35.0	26.5	28.0	32.5	33.0	28.0	36.0	31±3
	7	35.0	30.0	29.5	37.5	32.5	32.0	35.0	33±3
	Totals	235.5	187.0	198.5	239.0	251.5	234.5	227.5	224±25
1st Postoperative Week	1	5.0	12.0	53.0	5.0	11.0	6.0	39.5	15±19
	2	26.0	7.0	11.5	38.5	43.0	24.5	21.0	25±14
	3	47.0	15.0	34.5	39.0	35.0	35.0	10.5	34±11
	4	31.0	32.5	17.5	34.0	27.5	26.0	19.5	28±6
	5	24.5	24.0	24.5	31.5	37.0	35.0	16.5	29±6
	6	32.5	26.0	23.5	31.0	33.5	34.0	22.5	30±4
	7	44.0	38.0	28.0	32.0	40.0	38.0	28.0	37±6
	Totals	210.0	154.5	192.5	211.0	227.0	198.5	157.5	199±25
2nd Postoperative Week	1	35.0	40.5	32.0	38.5	26.5	45.0	26.5	38±4
	2	37.0	49.0	35.0	38.0	45.0	39.0	27.5	41±5
	3	35.0	55.0	34.5	39.0	44.0	46.0	26.5	42±8
	4	40.0	53.5	34.5	42.5	54.5	48.5	31.0	46±8
	5	37.0	41.0	35.5	44.0	48.5	40.0	34.5	41±5
	6	36.0	39.0	32.0	40.0	45.0	38.5	30.0	38±4
	7	40.0	46.5	33.5	42.5	51.5	37.5	28.5	42±6
	Totals	260.0	324.5	237.0	284.5	325.0	294.5	204.5	288±35

Contd./

Periods	Days	Experimental Group of Ss							
		A	B	C	D	E	F	G	Mean±SD
During 24hrs of Food Deprivation		45.0	54.0	12.0	30.0	34.5	68.0	6.0	41±20
24hrs of prandial Drinking following Food Deprivation		40.0	37.0	43.0	90.0	87.0	63.0	46.0	60±24
24hrs of Drinking (prandial) following Water Deprivation		61.0	68.5	44.5	61.0	84.5	60.5	44.0	63±13

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean±SD
Immediate Preoperative Week	1	37.0	25.0	25.0	23.0	25.0	26.0	27±5
	2	40.0	31.0	28.0	27.0	26.0	27.5	30±5
	3	35.5	25.0	25.0	19.0	22.0	24.0	25±6
	4	42.0	27.5	25.5	25.0	28.0	25.0	29±7
	5	36.0	25.0	26.0	25.0	29.0	24.5	28±4
	6	38.0	26.5	27.0	26.0	30.5	29.0	30±4
	7	36.5	29.0	28.0	26.0	29.5	28.5	30±4
	Totals	265.0	189.0	184.5	171.0	190.0	184.5	197±34
1st Postoperative Week	1	16.0	21.0	14.0	31.0	28.0	38.0	25±9
	2	30.0	27.0	24.5	30.5	30.0	29.0	29±2
	3	31.0	31.5	36.0	36.0	40.0	33.0	35±3
	4	30.0	25.0	33.0	31.5	37.0	29.0	31±4
	5	35.5	26.0	33.0	31.0	39.0	31.5	33±4
	6	35.0	31.5	30.0	31.0	37.0	31.0	33±3
	7	44.5	31.5	42.0	37.0	40.0	40.0	39±5
	Totals	222.0	193.5	212.5	228.0	251.0	231.5	223±19
2nd Postoperative Week	1	45.5	32.5	38.0	34.5	40.0	38.5	38±5
	2	40.5	34.5	36.0	35.5	37.0	38.0	39±4
	3	39.0	36.0	40.5	36.5	36.5	39.5	38±2
	4	40.0	36.5	39.5	34.5	36.0	35.0	27±2
	5	37.5	32.5	35.5	35.5	36.0	39.0	36±2
	6	40.0	36.0	32.5	34.0	48.5	33.5	37±6
	7	45.0	39.0	46.0	36.0	57.0	41.0	44±7
	Totals	287.5	247.0	278.0	246.5	291.0	264.5	269±20

Contd./

Periods	Days	Control Group of Ss						
		A	B	C	D	E	F	Mean±SD
During 24hrs of Food Deprivation		38.0	33.0	13.5	31.0	27.0	26.5	28±8
24hrs of prandial Drinking following Food Deprivation		43.5	41.0	31.5	40.0	61.0	46.0	44±10
24hrs of Drinking (prandial) following Water Deprivation		57.0	53.0	60.5	52.5	53.5	57.0	56±3

A D D E N D A

ADDENDUM

TO

THE

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ADDENDUM TO THE APPENDIX

Raw data from the experiments reported
in Chapters 3, 4, 5, 6 and 7

CHAPTER 3

An investigation into the involvement of the nigrostriatal dopamine system in feeding, sensorimotor function, motivation, rotational behaviour and learning

		1 Wk Pre-op			1st Post-op Wk			2nd Post-op Wk		
		Start	End	Wt Gain	Start	End	Wt Gain	Start	End	Wt Gain
Experimental (6-OHDA) Subjects	A	147.00g	175.00g	28.00g	160.30g	184.60g	24.30g	187.60g	211.90g	24.30g
	B	144.00	176.50	32.50	156.00	178.70	22.20	178.60	199.30	21.70
	C	151.00	182.00	31.00	172.00	195.00	23.00	198.40	229.10	30.70
	D	147.00	173.00	26.00	171.70	193.10	21.40	198.10	226.80	28.70
	E	152.00	181.60	29.60	175.00	185.30	10.30	191.20	200.10	8.90
	F	162.00	194.00	32.00	178.50	192.00	13.50	195.10	222.00	26.90
	G	160.30	188.50	28.20	174.00	184.60	10.60	190.60	218.80	28.20
	H	150.40	178.10	27.70	178.60	214.90	36.30	219.70	242.80	23.10
	$\bar{x} \pm$ SD	152± 6	181 ±7	29± 2	171± 8	191±11	20± 9	195±12	219±15	24± 7
Control (Vehicle) Subjects	*A	150.00	180.00	30.00	186.50	229.00	32.50	233.00	273.80	40.80
	*B	157.00	187.60	36.60	194.00	236.00	42.00	242.30	274.20	31.90
	*C	146.00	174.00	28.00	174.00	209.90	35.90	214.00	244.30	30.30
	D	146.80	178.20	31.40	180.80	216.00	35.50	225.40	249.10	23.70
	E	150.00	179.20	29.20	179.90	221.80	41.90	230.70	264.80	34.10
	F	149.90	186.00	36.10	187.80	232.30	44.50	242.20	290.00	47.80
	G	151.90	180.90	29.00	180.30	217.00	36.70	223.40	260.90	37.50
	H	148.00	176.50	28.50	177.00	222.10	45.10	232.00	257.50	25.50
	I	152.60	182.20	29.60	180.90	217.90	37.00	226.70	261.30	34.60
	$\bar{x} \pm$ SD	150± 3	181± 4	30± 2	182± 6	222± 8	39± 4	230± 9	264±14	34± 7

I Body weights of individual rats (6-OHDA lesioned and control rats) as recorded over the various stages of the experiment.

Abbreviations: Pre-op, before surgery; Post-op, after surgery; Wk, Week; Start, starting weight in the period indicated; End, final weight.

* partially lesioned control rats

		1 Wk Pre-op			1st Post-op Wk			2nd Post-op Wk			14th Post-op Wk		
		FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio
Experimental (6 - OHDA) Subjects	A	22.2g	170.9g	0.13	49.8g	105.6g	0.30	59.4g	204.6g	0.29	65.05g	228.25g	0.28
	B	27.6	176.8	0.16	68.1	162.2	0.42	110.5	248.6	0.44			
	C	22.4	171.2	0.13	32.3	146.7	0.22	50.2	218.8	0.23	46.35	220.35	0.21
	D	23.2	158.9	0.15	33.9	141.3	0.24	44.4	186.9	0.24	37.65	213.7	0.18
	E	19.7	170.6	0.12	48.2	148.4	0.32	39.4	167.2	0.24			
	F	25.2	179.1	0.14	116.1	217.8	0.53	139.3	289.4	0.48	69.1	262.0	0.26
	G	27.65	195.1	0.14	59.5	150.3	0.40	86.9	234.0	0.37	50.6	213.45	0.24
	H	23.0	164.4	0.14	77.6	227.5	0.34	96.0	272.5	0.35			
	Mean ± SD of Ratios			0.14±0.01			0.34± 0.1			0.33±0.1			0.23±0.04
Control (Vehicle) Subjects	*A	25.3	182.4	0.14	31.8	198.4	0.16	31.4	236.8	0.13			
	*B	40.1	203.4	0.20	30.8	218.1	0.14	32.9	239.8	0.14			
	*C	26.9	180.7	0.15	30.6	192.2	0.16	29.5	209.4	0.14			
	D	18.6	162.2	0.11	22.4	183.2	0.12	27.8	215.2	0.13	22.5	194.7	0.12
	E	27.0	163.8	0.16	38.8	197.7	0.20	43.3	247.4	0.18	33.85	240.05	0.14
	F	16.7	167.4	0.10	36.2	200.5	0.18	42.9	253.5	0.17	40.1	271.05	0.15
	G	20.4	162.5	0.13	34.8	179.9	0.19	45.3	235.2	0.19	39.1	246.1	0.16
	H	18.0	150.6	0.12	31.8	188.9	0.17	37.5	223.6	0.17	29.6	225.9	0.13
	I	32.8	178.8	0.18	27.2	169.9	0.16	39.7	227.3	0.17	41.8	243.3	0.17
	Mean ± SD of Ratios			0.14±0.03			0.16±0.02			0.16±0.02			0.15±0.03

II Ratios of food spilled to food bitten off in the process of feeding over various periods by individual rats (6 - OHDA lesioned and control rats).

Abbreviations: FS, food spilled; FM, food missing from the food hopper (i.e. food bitten off in the process of feeding).

* partially lesioned control Ss

		1 Wk Pre-op			1st Post-op Wk			2nd Post-op Wk			14th Post-op Wk		
		Fae	Foo	Ratio	Fae	Foo	Ratio	Fae	Foo	Ratio	Fae	Foo	Ratio
Experimental (6 - OHDA) Subjects	A	48.40g	148.70g	0.33	35.80g	115.80g	0.31	43.40g	145.20g	0.30	58.15g	163.20g	0.36
	B	48.41	149.20	0.32	37.70	94.10	0.40	47.20	138.10	0.34			
	C	53.80	148.80	0.36	35.00	114.40	0.31	55.70	168.60	0.33	67.20	174.00	0.39
	D	43.30	135.70	0.32	33.90	107.40	0.32	45.20	142.50	0.32	62.50	167.05	0.37
	E	52.70	150.90	0.35	30.90	100.20	0.31	39.70	127.80	0.31			
	F	58.90	153.90	0.38	35.50	101.70	0.35	46.90	150.10	0.31	71.10	192.90	0.37
	G	52.90	167.45	0.32	35.30	90.80	0.39	52.00	147.10	0.35	56.70	162.85	0.35
	H	62.10	141.40	0.44	51.80	149.90	0.35	68.90	176.50	0.39			
	Mean ± SD of Ratios			0.35±0.04			0.34±0.04			0.34±0.03			0.37±0.01
Control (Vehicle) Subjects	*A	52.60	156.10	0.34	63.40	166.70	0.38	73.30	205.40	0.36			
	*B	49.30	163.30	0.30	68.60	187.30	0.37	73.70	207.30	0.36			
	*C	51.30	153.80	0.33	53.20	161.60	0.33	56.40	179.90	0.31			
	D	51.10	143.60	0.36	58.30	161.80	0.36	75.90	187.40	0.41	70.70	172.20	0.41
	E	48.90	136.80	0.36	61.20	158.90	0.39	72.10	203.90	0.35	75.50	206.20	0.37
	F	59.70	150.70	0.40	64.80	164.30	0.39	86.90	210.60	0.41	89.50	230.95	0.39
	G	55.30	142.10	0.39	51.40	145.10	0.35	70.90	189.10	0.37	71.60	207.00	0.35
	H	47.50	132.60	0.36	55.40	157.10	0.35	66.30	186.10	0.36	70.85	196.30	0.36
	I	50.20	146.00	0.34	47.40	142.70	0.33	65.80	189.60	0.35	71.10	201.50	0.35
	Mean ± SD of Ratios			0.35±0.03			0.36±0.02			0.36±0.03			0.37±0.02

III Ratios of faeces passed to food ingested over various periods by individual rats (6 - OHDA lesioned and control rats)

Abbreviations: Fae, faeces passed; Foo, food ingested.

*Partially lesioned control rats

		Forepaw Use (effective)		Forepaw Use (abortive)		Total Number Effective Presses	Lever Choice		Rotations	
		1FP	CFP	1FP	CFP		1L	CL	1VR	CVR
Exp SS	1	136	0	5	0	136	0	136	5	1
	2	115	0	12	0	115	1	114	10	0
	3	120	2	2	0	120	116	4	26	0
	4	90	1	7	0	91	1	90	29	0
	5	116	0	4	0	116	115	1	10	0
	Mean ± SD	115±17	1±1	6±4	0	116±16	47±63	69±63	16±11	0
Control SS	1	0	170	0	11	170	168	2	1	0
	2	35	114	5	1	150	17	133	4	2
	3	218	0	10	0	206	218	0	0	2
	4	0	148	0	10	148	146	2	3	0
	5	85	55	18	5	143	136	7	1	6
	6	137	4	11	0	141	31	110	1	5
	Mean ± SD	79±86	82±73	7±7	5±5	162±29	119±79	42±62	2±2	3±3

IV Performance of individual rats trained to work for food in a two-lever Skinner box 12 weeks after 6 - OHDA or vehicle microinjection into the MFB on one side. The test session laster 20 minutes.

Abbreviations: IFP, ipsilateral forepaw; CFP, contralateral forepaw; IL, ipsilateral lever; CL, contralateral lever; IVR, ipsiversive rotation; CVR, contraversive rotation.

CHAPTER 4

Nigrostriatal dopaminergic control of operant behaviour, spatial behaviour and learning

		Pre-op		1 Wk Post-op		8 Wks Post-op	
		POPFP	POUFP	POPFP	POUFP	POPFP	POUFP
Contra-laterally lesioned SS	1	221	55	18	195	1	420
	2	389	2	11	55	7	330
	3	351	0	75	50	23	246
	4	129	47	16	88	3	157
	5	328	18	4	146	0	290
	6	328	77	63	128	0	359
	7	439	14	131	108	13	421
	8	451	20	17	50	43	166
	9	362	23	72	48	250	74
	Mean ±SD	333±102	28±26	45±43	96±52	38±81	274±122
Ipsi-laterally lesioned SS	1	340	1	372	1	450	2
	2	198	74	224	15	205	1
	3	198	76	283	7	291	0
	4	239	51	180	52	435	6
	5	279	42	102	4	369	1
	6	261	2	246	3	338	0
	7	273	36	219	2	259	2
	8	266	1	207	0	307	0
	Mean ±SD	248± 63	35±31	229±78	11±17	332±84	2±2
Control SS I	1	306	11	327	74	236	250
	2	252	53	236	175	393	22
	3	435	4	479	10	401	1
	4	241	42	234	95	316	47
	5	174	3	231	8	419	7
	6	256	11	332	6	411	10
	Mean ±SD	277±88	21±21	307±97	61±67	363±72	56±91
Control SS II	1	272	9	204	2	241	0
	2	290	65	341	76	368	81
	3	380	0	386	1	511	0
	4	350	1	413	0	400	0
	5	315	3	346	3	441	25
	6	440	0	472	0	421	1
	Mean ±SD	341±62	13±26	360±90	14±31	397±90	18±33

I Effective lever presses made with each forepaw by individual 6 - OHDA lesioned and control rats in 50 min. of testing, before surgery, 1 Wk postoperatively and 8 Wks postoperatively.

Abbreviations: Pre-op, preoperatively; post-op, postoperatively; POPFP, preoperatively preferred forepaw; POUFP, preoperatively unpreferred forepaw.

		Pre-op		1 Wk Post-op		8 Wks Post-op	
		POPFP	POUFP	POPFP	POUFP	POPFP	POUFP
Contra-laterally lesioned SS	1	37	25	1	74	0	54
	2	81	14	19	55	4	40
	3	21	13	11	29	3	77
	4	97	30	55	106	13	16
	5	10	5	13	43	0	83
	6	66	6	27	52	3	85
	7	52	7	10	22	3	25
	8	52	32	9	17	0	10
	9	78	30	25	52	39	12
	Mean ± SD	55±29	18±11	19±16	50±27	7±12	45±31
Ipsi-laterally lesioned SS	1	75	0	55	0	31	0
	2	10	13	28	14	30	1
	3	23	17	94	7	17	1
	4	29	21	81	14	30	3
	5	55	15	62	2	123	0
	6	21	0	33	1	33	0
	7	72	15	46	7	51	0
	8	35	1	46	0	19	0
	Mean ± SD	40±24	10±9	56±23	6±6	42±34	1±1
Control SS I	1	49	17	41	12	9	12
	2	44	28	78	15	20	8
	3	82	2	25	2	52	4
	4	96	6	5	1	17	1
	5	39	36	73	54	19	9
	6	74	14	79	4	29	0
	Mean ± SD	64±23	17±13	50±31	15±20	24±15	6±5
Control SS II	1	58	4	37	0	71	0
	2	103	2	26	0	28	0
	3	43	2	41	0	69	0
	4	81	43	42	11	47	26
	5	40	3	17	2	20	4
	6	148	1	50	0	78	2
	Mean ± SD	79±41	9±17	36±12	2±4	52±24	5±10

II Abortive presses made by individual 6 - OHDA lesioned and control rats in 50 mins. of testing, before surgery, 1 wk postoperatively and 8 wks postoperatively.

		Pre-op	1 wk post-op	8 wks post-op
Contralaterally lesioned SS	1	301	214	422
	2	393	67	337
	3	351	146	269
	4	202	104	161
	5	356	153	291
	6	423	201	359
	7	476	248	434
	8	486	70	324
	9	401	129	324
	Mean ± SD	377±88	148±63	312±90
Ipsilaterally lesioned SS	1	341	374	452
	2	345	244	206
	3	312	297	446
	4	445	241	284
	5	328	106	370
	6	263	249	338
	7	298	211	261
	8	267	207	307
	Mean ± SD	325±58	241±77	323±87
Control SS I	1	324	451	529
	2	318	434	417
	3	441	493	402
	4	290	361	389
	5	177	242	427
	6	346	339	425
	Mean ± SD	322±80	386±83	416±62
Control SS II	1	295	206	241
	2	418	481	536
	3	380	387	511
	4	353	413	400
	5	309	349	472
	6	442	469	422
	Mean ± SD	366±59	384±100	430±106

III Total number of effective lever presses executed by individual 6 - OHDA lesioned and control rats in 50 mins. of testing, before surgery, 1 wk postoperatively and 8 wks postoperatively

		Pre-op		1 Wk Post-op		8 wks Post-op	
		1L	CL	1L	CL	1L	CL
Contra-laterally lesioned SS	1	202	0	104	0	152	1
	2	343	13	140	13	116	175
	3	1	422	89	112	20	339
	4	470	7	242	6	120	314
	5	7	479	129	0	324	0
	6	401	0	68	11	34	179
	7	300	1	214	0	422	0
	8	0	393	37	30	8	329
	9	351	0	143	3	265	4
	Mean ±SD	231±185	146±215	130±66	19±36	162±145	149±152
Ipsi-laterally lesioned SS	1	341	0	374	0	448	4
	2	345	0	244	0	206	0
	3	0	312	20	275	4	442
	4	0	445	8	235	8	276
	5	318	10	106	0	362	8
	6	260	3	245	4	334	4
	7	194	124	97	124	110	151
	8	259	0	207	0	301	6
	Mean ±SD	191±150	138±181	145±128	112±146	197±173	135±171
Control SS I	1	154	170	429	19	417	112
	2	317	1	434	0	417	0
	3	440	1	483	10	394	8
	4	290	0	360	1	380	9
	5	177	0	240	2	427	0
	6	344	6	330	9	423	2
	Mean ±SD	287±107	30±69	379±88	7±7	410±19	22±44
Control SS II	1	280	5	206	0	241	0
	2	414	4	478	3	511	25
	3	379	1	379	8	510	1
	4	352	1	413	1	400	0
	5	309	11	329	20	422	50
	6	442	0	469	0	422	0
	Mean ±SD	363±62	4±4	379±101	5±8	418±99	13±21

IV Lever choice by individual 6 - OHDA lesioned and control rats preoperatively, 1 wk postoperatively and 8 wks postoperatively.

Abbreviations: 1L, Ipsilateral lever; CL, contralateral lever.

		Pre-op		1 Wk Post-op		8 Wks Post-op	
		IVR	CVR	IVR	CVR	IVR	CVR
Contra-	1	5	6	113	0	29	1
laterally	2	6	2	60	0	22	0
lesioned	3	1	1	178	0	6	1
SS	4	3	4	107	0	7	1
	5	3	3	55	0	7	0
	6	4	4	152	0	41	0
	7	1	1	80	0	19	0
	8	1	2	97	0	21	1
	9	2	1	131	0	8	0
Mean ± SD		3±2	3±2	108±41	0	18±12	0
Ipsi-	1	3	2	21	0	26	0
laterally	2	2	2	61	2	11	2
lesioned	3	1	0	112	0	16	0
SS	4	2	5	68	1	30	0
	5	0	1	118	0	45	0
	6	2	1	52	0	22	0
	7	1	1	69	0	10	1
	8	3	1	39	0	4	0
Mean ± SD		2±1	2±2	68±33	0	21±13	0
Control	1	1	5	3	6	4	2
SS	2	3	3	1	2	3	1
I	3	3	2	4	10	5	6
	4	1	1	2	2	2	3
	5	2	1	1	5	1	2
	6	5	4	3	4	2	0
Mean ± SD		3±2	3±2	2±1	5±3	3±1	2±2
	1	4	5	5	4	5	6
Control	2	0	4	3	6	2	1
SS	3	5	6	2	4	3	3
II	4	3	3	2	0	5	0
	5	2	2	2	2	6	0
	6	3	1	2	2	2	6
Mean ± SD		3±2	4±2	3±1	3±2	4±2	3±3

V Rotations in each direction in 50 mins. of testing, performed by 6 - OHDA lesioned and control rats preoperatively, 1 wk postoperatively and 8 wks postoperatively.

Abbreviations: IVR, ipsiversive rotations; CVR, contraversive rotations.

	Subjects	Side Choice POPS	POUS	Good rejections POPG	POUG	Av time per run (sec)
Pre-op	1	12	8	0	0	4.35
	2	12	8	2	0	6.58
	3	12	8	0	0	7.13
	4	13	7	0	0	4.58
	5	14	6	0	0	4.93
	6	12	8	0	0	3.45
	Mean ± SD	12±1	8±1	0	0	5±1
Post-op	1	7	13	1	0	5.23
	2	3	17	0	1	5.4
	3	6	14	0	3	4.68
	4	2	18	1	5	4.83
	5	4	16	0	4	7.23
	6	2	18	3	10	7.05
	Mean ± SD	4±2	17±2	1±1	4±4	6±1

VI Performance of individual rats in the T-maze.

Abbreviations: POPS, preoperatively preferred side; POUS, preoperatively unpreferred side; POPG, preoperatively preferred goal; POUG, preoperatively unpreferred goal.

	Forepaw use (effective)		Forepaw use (abortive)		Lever Choice		Rotations	
	IFP	CFP	IFP	CFP	IL	CL	IVR	CVR
1	5	118	9	17	3	122	13	0
2	1	99	1	29	101	0	126	0
3	57	4	24	12	7	52	82	0
4	65	24	26	6	82	13	17	0
Mean ± SD	32±34	61±56	15±12	16±10	48±51	47±55	60±54	0

VII Performance of individual rats trained ten days after a unilateral 6 - OHDA lesion of the MFB to work for food in a two-lever Skinner box. The test session lasted 25 mins.

CHAPTER 5

Postsynaptic dopamine receptor stimulation in rats with a unilateral nigrostriatal lesion: nigrostriatal dopaminergic control of sensorimotor versus spatial behaviour.

		No treatment		Apomorphine		Saline	
		POPFP	POUFP	POPFP	POUFP	POPFP	POUFP
Contralaterally	1	1	223	0	122	0	147
Lesioned	2	1	184	0	53	0	98
SS	3	2	172	1	70	2	147
	4	1	98	0	96	0	90
	5	0	228	0	60	0	40
	6	3	231	0	66	0	22
	7	43	112	0	54	0	26
	8	114	54	34	10	19	6
	Mean ± SD	21±40	163±67	4±12	66±33	3±7	72±56
Ipsilaterally	1	268	0	75	0	89	0
lesioned	2	178	0	122	1	177	0
SS	3	247	4	74	0	188	0
	4	202	1	47	0	70	0
	5	185	0	31	0	45	0
	6	162	0	40	0	60	0
	7	201	0	32	0	32	0
	Mean ± SD	206±38	1±1	60±33	0	94±63	0
Control	1	131	0	98	0	40	0
SS	2	205	36	161	0	258	0
	3	267	0	215	0	304	0
	4	238	0	142	83	188	50
	5	210	23	207	2	220	0
	6	191	0	227	0	284	0
	Mean ± SD	207±46	10±16	175±50	14±34	216±96	8±20

I Effective lever presses made with each forepaw by rats with a unilateral 6 - OHDA lesion of the nigrostriatal system and by vehicle-injected controls following i.p. adminstration of apomorphine or isotonic saline.

		No treatment		Apomorphine		Saline	
		POPFP	POUFP	POPFP	POUFP	POPFP	POUFP
Contralaterally lesioned SS	1	0	25	0	24	0	12
	2	1	25	0	7	0	0
	3	0	9	0	10	0	26
	4	0	48	0	46	0	15
	5	3	10	0	14	0	11
	6	5	3	0	8	0	4
	7	1	14	0	0	0	0
	8	0	20	4	5	0	2
	Mean ± SD	1±2	19±14	1±1	14±15	0	9±9
	Mean ±						
Ipsilaterally lesioned SS	1	10	0	10	0	22	0
	2	19	0	20	0	14	1
	3	4	0	0	0	2	1
	4	64	0	3	0	32	0
	5	12	0	4	0	12	0
	6	30	0	2	0	21	0
	7	12	0	3	0	3	0
	Mean ± SD	22±20	0	6±7	0	15±11	0
Control SS	1	24	0	8	0	15	0
	2	10	0	7	0	7	0
	3	22	0	17	0	28	0
	4	27	13	10	7	12	5
	5	12	4	1	0	3	1
	6	29	0	20	0	18	1
	Mean ± SD	21±8	3±5	11±7	1±3	14±9	1±2

II Abortive lever presses made with each forepaw by rats with a unilateral 6 - OHDA lesion of the nigrostriatal system and by vehicle-injected controls following i.p. administration of apomorphine or isotonic saline.

		No treatment		Apomorphine		Saline	
		IL	CL	IL	CL	IL	CL
Contralaterally lesioned SS	1	287	0	122	1	148	0
	2	0	187	0	53	2	96
	3	10	218	71	0	150	0
	4	25	209	96	0	90	0
	5	24	135	0	60	12	28
	6	224	0	1	66	0	22
	7	0	168	0	56	0	26
	8	174	0	44	0	21	4
	Mean ± SD	93±110	115±98	42±49	30±31	53±66	22±32
Ipsilaterally lesioned SS	1	268	0	73	2	84	0
	2	14	165	8	114	6	172
	3	6	152	0	74	0	188
	4	196	7	47	0	70	0
	5	183	2	25	6	45	0
	6	68	94	0	40	40	20
	7	199	2	32	0	6	26
	Mean ± SD	133±103	60±75	26±27	34±45	37±35	58±84
Control SS	1	131	0	98	0	40	0
	2	271	0	161	0	258	0
	3	266	1	215	0	304	0
	4	238	0	242	6	284	3
	5	188	49	191	19	211	11
	6	191	0	223	4	284	0
	Mean ± SD	214±54	8±20	188±52	5±7	230±99	2±4

III Lever choice displayed in a two-lever Skinner box by rats with a unilateral 6-OHDA lesion of the nigrostriatal system and by vehicle-injected controls, following i.p. administration of apomorphine or isotonic saline.

		No treatment		Apomorphine		Saline	
		IVR	CVR	IVR	CVR	IVR	CVR
Contralaterally	1	14	0	7	29	5	8
lesioned	2	13	0	2	90	2	8
SS	3	5	0	5	96	3	21
	4	3	0	10	36	11	10
	5	3	0	0	85	4	5
	6	19	0	0	109	0	0
	7	11	0	3	186	2	10
	8	9	0	4	106	16	1
	Mean ± SD	10±6	0	4±3	92±49	5±5	8±7
Ipsiversively	1	16	0	4	102	7	0
lesioned	2	4	0	5	50	8	19
SS	3	14	0	4	200	11	13
	4	32	0	0	125	12	22
	5	6	0	5	66	6	0
	6	7	0	0	104	2	0
	7	3	0	0	102	2	0
	Mean ± SD	12±10	0	3±2	107±48	7±4	8±10
Control	1	2	4	2	1	5	6
SS	2	1	0	0	1	3	2
	3	3	2	0	1	2	4
	4	2	0	1	0	7	0
	5	3	0	0	0	2	2
	6	1	4	1	2	2	2
	Mean ± SD	2±1	2±2	1±1	1±1	4±2	3±2

IV Rotations to each side performed during a 25 min. operant behaviour session by rats with a unilateral 6-OHDA lesion of the nigrostriatal system and by vehicle-injected controls, following i.p. administration of apomorphine or isotonic saline.

CHAPTER 6

Effects of pharmacological blockade of dopamine receptors on ingestive behaviour and body weight regulation

Periods		Pretreatment days 5 - 0			Treatment days 0 - 5			Treatment days 5 - 10		
		Start	End	Wt Gain	Start	End	Wt Gain	Start	End	Wt Gain
Experimental	A	173.40g	188.00g	18.30g	188.00g	205.90g	17.90g	205.90g	240.00g	14.10g
(haloperidel)	B	172.10	199.00	30.90	199.00	226.30	27.30	226.30	254.00	27.70
Subjects	C	156.10	172.90	18.10	172.90	197.80	24.90	197.80	215.00	17.20
	D	156.30	175.90	22.00	175.90	190.80	14.90	190.80	211.00	20.20
	E	150.40	172.60	23.90	172.60	187.70	15.10	187.70	209.00	21.30
	F	167.90	184.10	21.30	184.10	190.00	5.90	190.00	217.70	27.70
Mean ± SD		163±10	182±10	22±5	182±10	200±15	18±8	200±15	224±18	21±6
Control	A	164.20	175.50	14.70	175.50	187.50	12.00	187.50	220.20	32.70
(saline)	B	158.10	183.20	33.30	183.20	204.80	21.60	204.80	224.30	19.50
Subjects	C	173.40	197.10	29.20	197.10	217.00	19.90	217.00	241.90	24.90
	D	170.10	186.50	21.40	186.50	195.80	9.30	195.80	222.80	27.00
	E	173.70	188.70	20.50	188.70	219.00	30.30	219.00	243.80	24.80
	F	161.00	175.50	20.50	175.50	196.00	20.50	196.00	220.90	24.90
Mean ± SD		167±7	184±8	23±7	184±8	203±13	19±7	203±13	229±11	26±4

Periods		Treatment days 10 - 15		
		Start	End	Wt Gain
Experimental (haloperidol) Subjects	A	240.00g	257.50g	17.50g
	B	254.00	272.60	18.60
	C	215.00	229.50	14.50
	D	211.00	227.00	16.00
	E	209.00	218.90	9.90
	F	217.70	241.00	23.30
	Mean ± SD	274±18	241±20	17±4
Control (saline) Subjects	A	220.20	241.50	21.50
	B	224.30	240.70	16.40
	C	241.90	258.00	16.10
	D	222.80	251.00	28.20
	E	243.80	269.50	25.70
	F	220.90	241.20	20.30
	Mean ± SD	229±11	250±12	21±5

Periods		Treatment days 17 - 20			Treatment days 20 - 25			Post-treatment days 0 - 5		
		Start	End	Wt Gain	Start	End	Wt Gain	Start	End	Wt Gain
Experimental (haloperidol) Subjects	A	255.20g	272.60g	17.40g	272.60g	262.50g	-8.90g	262.50g	298.70g	36.20g
	B	269.20	285.00	15.80	285.00	301.00	16.00	301.00	315.90	14.90
	C	227.10	234.40	7.30	234.40	249.00	14.60	249.00	264.60	15.60
	D	222.00	228.20	6.20	228.20	239.10	11.00	239.10	256.20	17.10
	E	217.00	221.00	9.00	226.00	219.00	-7.00	219.00	239.15	20.15
	F	242.00	258.40	16.40	258.40	274.00	15.60	274.00	291.20	17.20
	Mean ± SD	239±20	251±25	12±5	251±25	257±29	7±12	257±29	278±29	20±8
Control (saline) Subjects	A	242.20	257.20	15.00	257.20	277.00	19.80	277.00	295.30	18.30
	B	237.00	252.00	15.00	252.00	264.20	12.20	264.20	286.35	22.15
	C	248.00	268.30	20.30	268.30	284.15	15.85	284.15	305.65	21.50
	D	250.30	260.70	10.40	260.70	283.00	22.30	283.00	301.80	18.80
	E	262.00	285.60	23.60	285.60	309.80	24.20	309.80	337.00	27.20
	F	241.30	254.10	12.80	254.10	275.10	21.00	275.10	197.90	22.80
	Mean ± SD	247±9	263±12	16±5	263±12	282±15	19±4	282±15	304±17	22±3

I Body weights of individual rats treated chronically with a moderately high dose of haloperidol (1mg/kg/day for 25 days) and of saline-treated controls, as recorded over the various stages of the experiment

Periods		Pretreatment days 5 - 0			Treatment days 0 - 5			Treatment days 5 - 10			Treatment days 10 - 15		
		FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio
Experimental (haloperidol) Subjects	A	24.1g	139.2g	0.17	34.0g	130.7g	0.02	19.7g	145.1g	0.14	15.7g	141.6g	0.11
	B	20.8	161.3	0.13	13.2	149.9	0.09	12.8	145.4	0.09	12.2	141.2	0.09
	C	19.7	134.1	0.15	15.8	137.4	0.11	16.9	134.9	0.13	17.3	126.15	0.14
	D	13.7	124.9	0.11	14.1	122.3	0.12	10.8	128.8	0.08	12.3	121.6	0.10
	E	16.3	131.5	0.12	11.2	130.7	0.09	10.5	133.9	0.08	10.3	119.2	0.09
	F	20.0	133.4	0.15	11.4	87.0	0.13	17.2	142.7	0.12	14.2	129.3	0.11
	Mean ± SD of ratios			0.14±0.02			0.12±0.04			0.11±0.04			0.11±0.03
Control (saline) Subjects	A	12.7	118.4	0.11	15.1	104.9	0.14	11.1	132.9	0.08	12.1	138.3	0.09
	B	21.9	142.4	0.15	19.8	138.1	0.14	18.4	139.2	0.13	17.3	136.4	0.13
	C	19.5	164.9	0.12	19.1	143.4	0.13	16.6	149.7	0.11	13.2	134.5	0.10
	D	15.4	135.9	0.11	16.3	115.9	0.14	14.1	137.6	0.10	15.5	151.2	0.10
	E	30.1	145.8	0.21	34.5	165.6	0.21	27.4	159.9	0.17	28.8	170.7	0.17
	F	25.1	128.9	0.19	33.6	136.0	0.2	25.9	139.3	0.19	19.5	139.2	0.14
	Mean ± SD of ratios			0.15±0.04			0.17±0.05			0.13±0.04			0.12±0.03

Periods		Treatment day 16 - 17 (24 hrs)			Treatment days 17 - 20			Treatment days 20 - 25			Post-treatment days 0 - 5		
		FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio
Experimental (haloperidol) Subjects	A	2.9	30.9g	0.09	9.1	79.1	0.12	11.1	130.9	0.08	18.2	157.05	0.12
	B	3.7	35.7	0.10	9.85	88.95	0.11	14.35	158.35	0.09	13.2	158.95	0.08
	C	5.5	34.0	0.16	11.05	79.8	0.14	17.7	146.85	0.12	19.5	147.75	0.13
	D	1.9	27.1	0.07	7.55	70.8	0.11	11.25	140.5	0.08	12.45	132.85	0.09
	E	3.8	27.3	0.14	6.8	65.4	0.1	10.1	107.15	0.09	9.1	122.8	0.07
	F	4.8	36.8	0.13	8.0	81.75	0.1	12.75	150.2	0.08	14.8	136.95	0.11
	Mean ± SD of Ratios			0.12±0.03			0.11±0.02			0.09±0.02			0.10±0.02
Control (saline) Subjects	A	3.2	35.5	0.09	7.2	86.4	0.08	12.4	159.05	0.08	16.15	162.6	0.10
	B	4.1	33.9	0.12	11.15	88.5	0.13	20.85	155.7	0.13	21.45	165.55	0.13
	C	3.0	32.4	0.09	8.75	93.05	0.09	14.1	164.5	0.09	18.85	171.95	0.11
	D	3.6	37.0	0.10	10.25	88.05	0.12	17.15	174.2	0.10	19.2	178.8	0.11
	E	6.8	37.8	0.18	14.9	102.8	0.14	26.4	188.35	0.14	29.4	200.7	0.15
	F	5.5	38.1	0.14	10.75	81.7	0.13	22.2	155.8	0.14	22.2	155.6	0.14
	Mean ± SD of Ratios			0.12±0.04			0.12±0.02			0.11±0.03			0.12±0.02

II Ratios of food spilled to food bitten off in the process of feeding over various periods by individual rats treated chronically with a moderately high dose of haloperidol (1mg/kg/day for 25 days) and by saline treated controls.

Periods		Pretreatment days 5 - 0			Treatment days 0 - 5			Treatment days 5 - 10			Treatment days 10 - 15		
		Fae	Foo	Ratio	Fae	Foo	Ratio	Fae	Foo	Ratio	Fae	Foo	Ratio
Experimental (haloperidol) Subjects	A	47.1g	115.1g	0.41	49.5g	90.7g	0.55	52.2g	125.4g	0.42	48.3g	125.9g	0.38
	B	56.0	140.5	0.40	57.3	109.77	0.52	58.1	132.6	0.44	51.5	129.0	0.40
	C	45.3	114.4	0.40	48.9	121.6	0.40	46.4	118.0	0.39	38.9	108.85	0.36
	D	41.2	111.2	0.37	39.8	108.2	0.37	44.91	118.0	0.38	38.1	109.3	0.35
	E	47.7	115.2	0.41	50.4	119.5	0.42	52.1	123.4	0.42	42.4	109.5	0.39
	F	48.3	113.4	0.43	36.7	75.6	0.49	63.3	125.5	0.50	48.9	115.1	0.42
Mean ± SD of ratios				0.40±0.02			0.41±0.07			0.43±0.04			0.38±0.03
Control (saline) Subjects	A	42.4	105.7	0.40	33.2	89.8	0.37	45.7	121.9	0.37	45.8	126.0	0.36
	B	43.8	119.5	0.37	45.3	118.3	0.38	47.1	120.8	0.39	45.0	121.1	0.37
	C	61.7	145.4	0.42	54.2	124.3	0.44	58.2	131.1	0.44	49.3	121.3	0.41
	D	47.4	120.5	0.39	39.9	99.6	0.40	47.8	123.5	0.39	49.7	135.7	0.37
	E	41.5	115.7	0.36	46.4	129.1	0.36	53.8	132.5	0.41	54.6	141.9	0.38
	F	43.1	101.8	0.42	56.1	96.4	0.58	56.3	113.4	0.50	49.5	119.7	0.41
Mean ± SD of ratios				0.39±0.03			0.42±0.08			0.42±0.05			0.38±0.02

Periods		Treatment days 17 - 20			Treatment days 20 - 25			Post-treatment days 0 - 5		
		Fae	Foo	Ratio	Fae	Foo	Ratio	Fae	Foo	Ratio
Experimental (haloperidol) Subjects	A	23.1	70.00g	0.33	47.4g	119.8g	0.40	46.15g	138.85	0.33
	B	28.55	79.1	0.36	61.25	144.05	0.43	55.15	145.75	0.38
	C	24.1	68.75	0.35	47.3	129.15	0.37	45.3	128.25	0.35
	D	23.1	63.25	0.37	48.15	129.25	0.37	44.5	120.4	0.37
	E	20.3	58.6	0.35	35.35	97.05	0.36	43.3	113.7	0.39
	F	34.0	74.75	0.45	58.95	137.45	0.43	46.75	122.15	0.38
Mean ± SD of ratios				0.37±0.04			0.39±0.03			0.37±0.02
Control (saline) Subjects	A	26.85	79.2	0.34	52.3	146.35	0.36	47.6	146.45	0.33
	B	26.25	77.35	0.34	50.3	134.85	0.37	47.85	144.1	0.33
	C	33.4	84.3	0.40	63.6	150.4	0.42	61.4	153.1	0.40
	D	28.2	77.8	0.36	57.8	157.05	0.37	53.85	159.6	0.34
	E	30.75	87.9	0.35	62.4	161.95	0.39	64.95	171.3	0.38
	F	27.4	70.95	0.39	60.6	133.9	0.45	48.8	133.4	0.37
Mean ± SD of ratios				0.36±0.03			0.39±0.04			0.36±0.03

III Ratios of faeces passed to food ingested over various periods by individual rats chronically treated with a moderately high dose of haloperidol (1 mg/kg/day for 25 days) and by saline-treated controls

Periods		Pretreatment days 3 - 0			Treatment days 0 - 3			Post-treatment days 0 - 3		
		Start	End	Wt Gain	Start	End	Wt Gain	Start	End	Wt Gain
Experimental (haloperidol) Subjects	A	154.80g	169.90g	15.10g	169.90g	175.40g	5.50g	175.40g	187.60g	12.20g
	B	148.30	163.65	15.35	163.65	166.40	2.75	166.40	178.70	12.30
	C	148.60	160.80	12.20	160.80	164.80	4.00	164.80	181.10	16.30
	D	140.80	150.90	10.10	150.90	155.80	4.90	155.80	168.00	12.20
	E	150.10	162.85	12.75	162.85	164.70	1.85	164.70	180.40	15.70
	F	151.00	159.90	8.90	159.90	160.90	1.00	160.90	174.30	13.40
	Mean ± SD	149±5	161±6	12±3	161±6	165±6	3±2	165±6	178±7	14±2
Control (saline) Subjects	A	151.10	166.40	15.30	166.40	181.80	15.40	181.80	197.90	16.10
	B	141.60	158.90	17.30	158.90	176.00	17.10	176.00	192.60	16.60
	C	148.00	159.00	11.00	159.00	173.00	14.00	173.00	193.60	20.60
	D	147.00	160.20	13.20	160.20	174.20	14.00	174.20	190.10	15.90
	E	145.00	160.50	15.50	160.50	181.00	20.50	181.00	194.40	13.40
	F	150.00	162.90	12.90	162.90	177.95	15.05	177.95	199.10	11.15
	Mean ± SD	147±3	161±3	14±2	161±3	177±4	16±2	177±4	195±3	16±3

IV Body weights of individual rats treated chronically with a very high dose of haloperidol (10 mg/kg/day for 3 days) and of saline-treated controls, as recorded over the various stages of the experiment.

Periods		Pretreatment days 3 - 0			Treatment days 0 - 3			Post-treatment days 0 - 3		
		FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio
Experimental (haloperidol) Subjects	A	6.10g	65.20g	0.09	4.85g	60.05g	0.08	4.25g	66.8g	0.06
	B	6.45	70.00	0.09	6.2	61.90	0.10	5.95	70.40	0.08
	C	12.95	76.80	0.17	7.0	63.60	0.11	9.1	77.10	0.12
	D	8.30	70.75	0.12	5.3	57.40	0.09	7.0	69.90	0.10
	E	5.50	78.55	0.07	3.0	59.15	0.05	3.7	73.70	0.05
	F	6.75	64.75	0.10	4.15	55.85	0.07	4.3	67.20	0.06
Mean ± SD of ratios				0.11±0.04			0.08±0.02			0.08±0.03
Control (saline) Subjects	A	7.10	65.05	0.11	9.0	72.05	0.12	7.05	72.40	0.10
	B	6.90	67.55	0.10	8.0	76.25	0.10	8.0	76.05	0.11
	C	7.35	68.30	0.11	9.55	74.35	0.13	7.65	76.50	0.10
	D	10.95	75.50	0.15	13.1	82.50	0.16	10.65	79.40	0.13
	E	10.15	71.55	0.14	8.7	79.55	0.11	7.55	79.80	0.09
	F	13.10	75.40	0.17	10.8	83.15	0.13	12.35	89.60	0.14
Mean ± SD of ratios				0.13±0.03			0.13±0.02			0.11±0.02

Periods		Post-treatment Period (1½ hrs of feeding saline)			Post-treatment Period (1½ hrs of feeding, Apomorphine 0.1 mg/kg)			Post-treatment Period (1½ hrs of feeding, Apomorphine, 1.0 mg/kg)		
		FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio
Experimental (haloperidol) Subjects	A	0.30g	4.10g	0.07	0.40g	5.10g	0.08	0.40	2.80g	0.14
	B	0.050	2.20	0.02	0.25	2.80	0.09	0.40	2.65	0.15
	C	0.90	5.60	0.16	0.45	4.10	0.11	0.35	2.90	0.12
	D	0.05	1.60	0.03	0.10	0.90	0.11	0.10	1.45	0.07
	E	0.10	4.35	0.02	0.35	5.20	0.07	0.10	2.20	0.05
	F	0.20	3.90	0.05	0.20	2.85	0.07	0.05	1.80	0.03
Mean ± SD of ratios				0.06±0.05			0.09±0.02			0.09±0.05
Control (saline) Subjects	A	0.35	3.55	0.10	0.10	2.70	0.04	0.35	3.25	0.11
	B	0.85	7.00	0.12	1.25	5.85	0.21	0.50	3.60	0.14
	C	0.05	2.50	0.02	0.20	3.20	0.06	0.10	1.10	0.09
	D	0.13	6.40	0.05	0.95	4.00	0.24	0.35	4.40	0.08
	E	0.35	3.65	0.10	0.90	4.05	0.22	0.70	4.35	0.16
	F	0.10	1.20	0.08	0.10	1.35	0.07	0.10	1.55	0.06
Mean ± SD of ratios				0.08±0.04			0.14±0.09			0.11±0.04

V Ratios of food spilled to food bitten off in the process of feeding over various periods by individual rats treated chronically with a very high dose of haloperidol (10 mg/kg/day for 3 days) and by saline-treated controls.

Periods		Pretreatment days 3 - 0			Treatment days 0 - 3			Post-treatment days 0 - 3		
		Fae	Foo	Ratio	Fae	Foo	Ratio	Fae	Foo	Ratio
Experimental (haloperidol) Subjects	A	17.9g	59.1g	0.30	17.2g	55.2g	0.31	25.6g	62.55g	0.41
	B	18.85	63.55	0.30	17.9	55.7	0.32	21.4	64.45	0.33
	C	19.0	63.85	0.30	19.55	56.6	0.35	23.7	68.0	0.35
	D	20.9	62.45	0.33	17.7	52.1	0.34	23.5	62.9	0.37
	E	22.9	73.05	0.31	16.1	56.15	0.29	23.95	70.0	0.34
	F	16.9	58.0	0.29	15.6	51.7	0.30	19.75	62.9	0.31
Mean ± SD of ratios			0.31±0.01			0.32±0.02				0.35±0.03
Control (saline) Subjects	A	17.9	57.95	0.31	17.55	63.05	0.28	23.05	65.35	0.35
	B	17.65	60.65	0.29	23.6	68.25	0.35	23.25	68.05	0.34
	C	19.9	60.95	0.33	20.2	64.8	0.31	21.2	68.85	0.31
	D	18.7	64.55	0.29	21.95	69.4	0.32	20.9	68.75	0.30
	E	17.05	61.4	0.28	20.7	70.85	0.29	24.4	72.25	0.34
	F	17.65	62.3	0.28	22.45	72.35	0.31	22.2	77.25	0.29
Mean ± SD of ratios				0.30±0.02			0.31±0.02			0.32±0.02

VI Ratios of faeces passed to food ingested over various periods by individual rats chronically treated with a very high dose of haloperidol (10 mg/kg/day for 3 days) and by saline-treated controls.

CHAPTER 7

Behavioural effects of unilateral kainate lesion of the striatum

		1 Wk Pre-op			1st Post-op Wk			2nd Post-op Wk		
		Start	End	Wt Gain	Start	End	Wt Gain	Start	End	Wt Gain
Experimental (kainic acid) Subjects	A	158.30g	188.70g	30.40g	161.20g	200.80	39.60g	200.80g	238.20g	37.40g
	B	158.10	193.40	35.30	141.90	173.10	31.20	173.10	222.90	49.80
	C	164.90	191.70	26.80	147.20	174.30	27.10	174.30	213.40	39.10
	D	161.80	199.70	37.90	179.30	213.00	33.70	213.00	253.50	40.50
	E	172.50	198.00	25.50	189.30	223.00	33.70	223.00	263.50	40.50
	F	166.40	191.10	24.70	166.20	216.80	50.60	216.80	255.30	38.50
	*G	168.00	202.40	34.4	167.90	183.50	15.60	183.50	228.30	44.80
Mean ± SD		164±5	194±4	30±5	164±18	200±22	36±8	200±22	241±20	41±4
Control (vehicle) Subjects	A	152.10	180.60	28.50	177.70	205.70	28.00	205.70	232.70	27.00
	B	151.70	174.40	22.70	178.90	203.00	24.10	203.00	229.20	26.20
	C	161.70	188.90	27.20	187.40	219.10	31.70	219.10	248.90	29.80
	D	160.00	188.70	28.70	189.50	225.70	36.20	225.70	255.00	29.30
	E	161.80	192.30	30.50	192.70	221.80	29.10	221.80	239.70	17.90
	F	158.20	198.50	40.30	202.70	245.30	42.60	245.30	285.10	39.80
Mean ± SD		158±5	187±9	30±6	188±9	220±15	32±7	220±15	248±20	28±7

I Body weights of individual rats (kainic acid experimental and vehicle-injected control rats), as recorded over the various stages of the experiment

* Subject excluded from data analysis because of pallidal damage.

		1 Wk Pre-op			1st Post-op Wk			2nd Post-op Wk		
		FS	FM	Ratio	FS	FM	Ratio	FS	FM	Ratio
Experimental	A	22.66 g	162.4g	0.14	39.31g	162.3g	0.24	59.82	257.9g	0.23
(kainic acid)	B	13.37	162.7	0.08	9.27	73.2	0.13	76.61	273.9	0.28
Subjects	C	25.43	166.8	0.15	25.68	92.5	0.28	30.81	208.7	0.15
	D	13.29	165.5	0.08	17.92	140.7	0.13	39.81	234.3	0.17
	E	19.59	156.0	0.13	25.94	151.0	0.17	41.02	226.4	0.21
	F	21.94	169.6	0.13	30.31	136.1	0.22	49.76	243.5	0.20
	*G	13.25	165.2	0.08	58.63	129.6	0.45	48.06	220.1	0.22
Mean ± SD of ratios				0.12±0.03			0.20±0.06			0.21±0.05
	A	31.37	172.2	0.18	22.61	148.0	0.15	29.88	205.6	0.15
Control	B	15.1	143.1	0.11	19.14	162.3	0.12	25.44	198.6	0.13
(vehicle)	C	22.18	172.5	0.13	28.23	179.0	0.16	38.14	246.9	0.15
Subjects	D	17.49	157.6	0.11	21.36	180.1	0.12	22.95	214.0	0.11
	E	18.52	165.6	0.11	26.81	179.1	0.15	26.82	211.3	0.13
	F	15.96	190.7	0.08	14.35	188.3	0.08	21.73	246.4	0.09
Mean ± SD of ratios				0.12±0.03			0.13±0.03			0.13±0.03

II Ratios of food spilled to food bitten off in the process of feeding over various periods by individual rats (kainic acid experimental and vehicle-injected control rats)

* Subject excluded from data analysis because of pallidal damage

		1 Wk Pre-op			1st Post-op Wk			2nd Post-op Wk		
		Fae	Foo	Ratio	Fae	Foo	Ratio	Fae	Foo	Ratio
Experimental (kainic acid) Subjects	A	48.27g	139.74g	0.35	44.46g	122.99g	0.36	72.56g	198.08g	0.37
	B	46.36	149.33	0.31	26.26	63.93	0.41	85.84	197.29	0.44
	C	52.17	141.37	0.37	17.45	66.82	0.26	66.4	177.89	0.37
	D	56.35	152.21	0.37	47.45	122.78	0.39	73.5	194.49	0.38
	E	48.98	136.41	0.36	41.11	125.06	0.33	67.41	185.38	0.36
	F	54.78	146.94	0.37	37.12	105.79	0.35	73.02	193.74	0.38
	*G	60.07	151.95	0.40	19.49	70.97	0.27	59.78	172,04	0.35
Mean ± SD of ratios				0.36±0.02			0.37±0.05			0.38±0.03
Control (vehicle) Subjects	A	53.17	140.23	0.38	60.14	125.29	0.48	88.0	175.72	0.50
	B	41.94	128.00	0.33	52.95	143.16	0.37	70.16	173.16	0.41
	C	47.28	150.32	0.31	59.92	150.77	0.40	88.0	208.76	0.42
	D	42.79	140.11	0.31	59.14	158.74	0.37	68.47	191.05	0.36
	E	47.62	147.08	0.32	75.41	152.29	0.50	70.12	184.48	0.38
	F	57.89	174.74	0.33	63.87	173.95	0.37	79.21	224.47	0.35
Mean ± SD of ratios				0.33±0.03			0.4±0.06			0.4±0.05

III Ratios of faeces passed to food ingested over various periods by individual rats (kainic acid experimental and vehicle-injected rats)

* Subject excluded from data analysis because of pallidal damage

	Subjects	Forepaw use (effective)		Forepaw use (abortive)		Total number effective presses	Lever Choice		Rotations	
		POPFP	POUFP	POPFP	POUFP		IL	CL	IVP	CVR
Pre-op	1	398	15	41	6	413	402	11	4	1
	2	292	167	116	109	431	430	2	1	2
	3	569	8	66	4	579	557	22	6	6
	4	178	175	43	76	405	404	2	2	3
	5	407	10	148	3	425	17	408	2	4
	6	277	68	62	25	385	383	2	5	1
	*7	194	160	35	15	415	29	387	3	9
	Mean ± SD	331±138	86±79	73±43	34±42	436±65	317±209	119±190	3±2	4±3
1 Wk Post-op	1	127	369	59	53	529	16	513	15	1
	2	43	263	5	25	317	144	175	38	6
	3	98	211	14	22	317	56	262	12	12
	4	29	129	9	70	163	148	16	9	1
	5	50	186	21	52	241	33	208	2	7
	6	34	208	5	185	249	246	3	21	0
	*7	19	365	5	41	384	34	350	14	1
	Mean± SD	57±40	247±91	17±20	64±56	314±118	97±85	218±180	16±11	4±4

IV Performance of individual rats before and 1 Wk after a unilateral kainate or saline microinjection into the striatum. The task was food-rewarded lever pressing and was set in a two-lever Skinner box. There were two sessions of 25 mins each on two consecutive days before and then 1 Wk after surgery.

* Subject was excluded from data analysis because of substantial loss of "limbic forebrain" dopamine.